Attorney Docket No.

# UTILITY **PATENT APPLICATION TRANSMITTAL**

First Inventor or Application Identifier Title

Steven G. Reed

COMPOSITIONS AND METHODS FOR THE THERAPAC

AND DIAGNOSIS OF LUNG CANCER

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See i	APPLICATION ELEMENTS  MPEP chapter 600 concerning utility patent application contents.	ADDRESS TO:  Box Patent Application Assistant Commissioner for Pater Washington, D.C. 20231
1. 2. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1.	General Authorization Form & Fee Transmittal (Submit an original and a duplicate for fee processing)  Specification [Total Pages] (preferred arrangement set forth below)  Descriptive Title of the Invention Cross References to Related Applications Statement Regarding Fed sponsored R & D Reference to Microfiche Appendix Background of the Invention  Brief Summary of the Invention Brief Description of the Drawings (if filed) Detailed Description Claim(s) Abstract of the Disclosure  Drawing(s) (35 USC 113) [Total Sheets]	Microfiche Computer Program (Appendix)  Nucleotide and Amino Acid Sequence Submission (if applicable, all necessary)  a.
	a. Newly executed (original or copy)  b. Copy from a prior application (37 CFR 1.63(d)) (for continuation/divisional with Box 17 completed)  i. DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b) Incorporation By Reference (useable if box 4b is checked) The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered to be part of the disclosure of the accompanying application and is hereby incorporated by reference therein.	12. Preliminary Amendment  13. X Return Receipt Postcard  14. Small Entity Statement filed in prior application, Status still proper and desired  15. Certified Copy of Priority Document(s) (if foreign pnority is claimed)  16. X Other: Certificate of Express Mail
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	Continuation Divisional X Continuation-In-In-In-In-In-In-In-In-In-In-In-In-In	Part (CIP) of prior Application No.: 09/640,878  Group / Art Unit not assigned
	Claims the benefit of Provisional Application No.	
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Respectfully submitted,  TYPED or PRINTED NAME		

SIGNATURE

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## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Date

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**PATENT** 

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# CERTIFICATE OF MAILING BY "EXPRESS MAIL"

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Respectfully submitted,

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Enclosures:

Postcard

Form PTO/SB/05

Specification, Claims, Abstract (137 pages)

Sequence Listing (217 pages)

Declaration for Sequence Listing

Diskette for Sequence Listing

Information Disclosure Statement

Form PTO-1449

Cited References (11)

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# COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF LUNG CANCER

#### 5 REFERENCE TO RELATED APPLICATIONS

This application is related to U.S. Patent Application No. 09/640,878, filed August 18, 2000; U.S. Patent Application No. 09/588,937, filed May 26, 2000; U.S. Patent Application No. 09/538,037, filed March 29, 2000; U.S. Patent Application No. 09/518,809, filed March 3, 2000; U.S. Patent Application No. 09/476,235 filed December 30, 1999; U.S. Patent Application No. 09/370,838, filed August 9, 1999; and U.S. Patent Application No. 09/285,323, filed April 2, 1999, each a CIP of the previous application and all pending, and PCT/US00/08560, filed March 30, 2000, pending.

#### TECHNICAL FIELD OF THE INVENTION

The present invention relates generally to therapy and diagnosis of cancer, such as lung cancer. The invention is more specifically related to polypeptides comprising at least a portion of a lung tumor protein, and to polynucleotides encoding such polypeptides. Such polypeptides and polynucleotides may be used in compositions for prevention and treatment of lung cancer, and for the diagnosis and monitoring of such cancers.

# 20 BACKGROUND OF THE INVENTION

Lung cancer is the primary cause of cancer death among both men and women in the U.S., with an estimated 172,000 new cases being reported in 1994. The five-year survival rate among all lung cancer patients, regardless of the stage of disease at diagnosis, is only 13%. This contrasts with a five-year survival rate of 46% among cases detected while the disease is still localized. However, only 16% of lung cancers are discovered before the disease has spread.

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Early detection is difficult since clinical symptoms are often not seen until the disease has reached an advanced stage. Currently, diagnosis is aided by the use of chest x-rays, analysis of the type of cells contained in sputum and fiberoptic examination of the bronchial passages. Treatment regimens are determined by the type and stage of the cancer, and include surgery, radiation therapy and/or chemotherapy. In spite of considerable research into therapies for the disease, lung cancer remains difficult to treat.

Accordingly, there remains a need in the art for improved vaccines, treatment methods and diagnostic techniques for lung cancer.

#### SUMMARY OF THE INVENTION

Briefly stated, the present invention provides compositions and methods for the diagnosis and therapy of cancer, such as lung cancer. In one aspect, the present invention provides polypeptides comprising at least a portion of a lung tumor protein, or a variant thereof. Certain portions and other variants are immunogenic, such that the ability of the variant to react with antigen-specific antisera is not substantially diminished. Within certain embodiments, the polypeptide comprises a sequence that is encoded by a polynucleotide sequence selected from the group consisting of: (a) sequences recited in SEQ ID NOs:217-390, 392, 394, 396, 398-420 and 422-424; (b) variants of a sequence recited in SEQ ID NOs:217-390, 392, 394, 396, 398-420 422-424, 428-433 and 440; and (c) complements of a sequence of (a) or (b). In specific embodiments, the polypeptides of the present invention comprise at least a portion of a tumor protein that includes an amino acid sequence selected from the group consisting of sequences recited in SEQ ID NOs:391, 393, 395, 397, 421, 425-427, 434-439 and variants thereof.

The present invention further provides polynucleotides that encode a polypeptide as described above, or a portion thereof (such as a portion encoding at least 15 amino acid residues of a lung tumor protein), expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

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Within other aspects, the present invention provides pharmaceutical compositions comprising a polypeptide or polynucleotide as described above and a physiologically acceptable carrier.

Within a related aspect of the present invention, immunogenic compositions, or vaccines for prophylactic or therapeutic use are provided. Such compositions comprise a polypeptide or polynucleotide as described above and an immunostimulant.

The present invention further provides pharmaceutical compositions that comprise: (a) an antibody or antigen-binding fragment thereof that specifically binds to a lung tumor protein; and (b) a physiologically acceptable carrier.

Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a pharmaceutically acceptable carrier or excipient. Antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B cells.

Within related aspects, immunogenic compositions, or vaccines, are provided that comprise: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) an immunostimulant.

The present invention further provides, in other aspects, fusion proteins that comprise at least one polypeptide as described above, as well as polynucleotides encoding such fusion proteins.

Within related aspects, pharmaceutical compositions comprising a fusion protein, or a polynucleotide encoding a fusion protein, in combination with a physiologically acceptable carrier are provided.

Compositions are further provided, within other aspects, that comprise a fusion protein, or a polynucleotide encoding a fusion protein, in combination with an immunostimulant.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient a composition as recited above. The patient may be afflicted with lung cancer, in which case

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the methods provide treatment for the disease, or patient considered at risk for such a disease may be treated prophylactically.

The present invention further provides, within other aspects, methods for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a lung tumor protein, wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the protein from the sample.

Within related aspects, methods are provided for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated as described above.

Methods are further provided, within other aspects, for stimulating and/or expanding T cells specific for a lung tumor protein, comprising contacting T cells with one or more of: (i) a polypeptide as described above; (ii) a polypucleotide encoding such a polypeptide; and/or (iii) an antigen presenting cell that expresses such a polypeptide; under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Isolated T cell populations comprising T cells prepared as described above are also provided.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population as described above.

The present invention further provides methods for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells isolated from a patient with one or more of: (i) a polypeptide comprising at least an immunogenic portion of a lung tumor protein; (ii) a polynucleotide encoding such a polypeptide; and (iii) an antigen-presenting cell that expressed such a polypeptide; and (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient. Proliferated cells may, but need not, be cloned prior to administration to the patient.

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Within further aspects, the present invention provides methods for determining the presence or absence of a cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and (c) comparing the amount of polypeptide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within preferred embodiments, the binding agent is an antibody, more preferably a monoclonal antibody. The cancer may be lung cancer.

The present invention also provides, within other aspects, methods for monitoring the progression of a cancer in a patient. Such methods comprise the steps of:

(a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polypeptide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

The present invention further provides, within other aspects, methods for determining the presence or absence of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a lung tumor protein; (b) detecting in the sample a level of a polynucleotide, preferably mRNA, that hybridizes to the oligonucleotide; and (c) comparing the level of polynucleotide that hybridizes to the oligonucleotide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within certain embodiments, the amount of mRNA is detected via polymerase chain reaction using, for example, at least one oligonucleotide primer that hybridizes to a polynucleotide encoding a polypeptide as recited above, or a complement of such a polynucleotide. Within other embodiments, the amount of mRNA is detected using a hybridization technique, employing an

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oligonucleotide probe that hybridizes to a polynucleotide that encodes a polypeptide as recited above, or a complement of such a polynucleotide.

In related aspects, methods are provided for monitoring the progression of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a lung tumor protein; (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polynucleotide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

Within further aspects, the present invention provides antibodies, such as monoclonal antibodies, that bind to a polypeptide as described above, as well as diagnostic kits comprising such antibodies. Diagnostic kits comprising one or more oligonucleotide probes or primers as described above are also provided.

These and other aspects of the present invention will become apparent upon reference to the following detailed description. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

# SEQUENCE IDENTIFIERS

SEQ ID NO: 1 is the determined cDNA sequence for L363C1.cons

SEQ ID NO: 2 is the determined cDNA sequence for L263C2.cons

SEQ ID NO: 3 is the determined cDNA sequence for L263C2c

SEQ ID NO: 4 is the determined cDNA sequence for L263C1.cons

SEQ ID NO: 5 is the determined cDNA sequence for L263C1b

SEQ ID NO: 6 is the determined cDNA sequence for L164C2.cons

SEQ ID NO: 7 is the determined cDNA sequence for L164C1.cons

SEQ ID NO: 8 is the determined cDNA sequence for L366C1a

SEQ ID NO: 9 is the determined cDNA sequence for L260C1.cons

SEQ ID NO: 10 is the determined cDNA sequence for L163C1c

SEQ ID NO: 11 is the determined cDNA sequence for L163C1b

- SEQ ID NO: 12 is the determined cDNA sequence for L255C1.cons SEQ ID NO: 13 is the determined cDNA sequence for L255C1b SEQ ID NO: 14 is the determined cDNA sequence for L355C1.cons SEQ ID NO: 15 is the determined cDNA sequence for L366C1.cons SEQ ID NO: 16 is the determined cDNA sequence for L163C1a SEQ ID NO: 17 is the determined cDNA sequence for LT86-1 SEQ ID NO: 18 is the determined cDNA sequence for LT86-2 SEQ ID NO: 19 is the determined cDNA sequence for LT86-3 SEQ ID NO: 20 is the determined cDNA sequence for LT86-4 10 SEQ ID NO: 21 is the determined cDNA sequence for LT86-5 SEQ ID NO: 22 is the determined cDNA sequence for LT86-6 SEQ ID NO: 23 is the determined cDNA sequence for LT86-7 SEQ ID NO: 24 is the determined cDNA sequence for LT86-8 SEQ ID NO: 25 is the determined cDNA sequence for LT86-9 15 SEQ ID NO: 26 is the determined cDNA sequence for LT86-10 SEQ ID NO: 27 is the determined cDNA sequence for LT86-11 SEQ ID NO: 28 is the determined cDNA sequence for LT86-12 SEQ ID NO: 29 is the determined cDNA sequence for LT86-13 SEQ ID NO: 30 is the determined cDNA sequence for LT86-14 20 SEQ ID NO: 31 is the determined cDNA sequence for LT86-15 SEQ ID NO: 32 is the predicted amino acid sequence for LT86-1
- SEQ ID NO: 32 is the predicted amino acid sequence for LT86-2 SEQ ID NO: 34 is the predicted amino acid sequence for LT86-3 SEQ ID NO: 35 is the predicted amino acid sequence for LT86-4 SEQ ID NO: 36 is the predicted amino acid sequence for LT86-5 SEQ ID NO: 37 is the predicted amino acid sequence for LT86-6 SEQ ID NO: 38 is the predicted amino acid sequence for LT86-7 SEQ ID NO: 39 is the predicted amino acid sequence for LT86-8

SEQ ID NO: 40 is the predicted amino acid sequence for LT86-9

- SEQ ID NO: 42 is the predicted amino acid sequence for LT86-11
- SEQ ID NO: 43 is the predicted amino acid sequence for LT86-12
- SEQ ID NO: 44 is the predicted amino acid sequence for LT86-13
- SEQ ID NO: 45 is the predicted amino acid sequence for LT86-14
- 5 SEQ ID NO: 46 is the predicted amino acid sequence for LT86-15
  - SEQ ID NO: 47 is a (dT)<sub>12</sub>AG primer
  - SEQ ID NO: 48 is a primer
  - SEQ ID NO: 49 is the determined 5' cDNA sequence for L86S-3
  - SEQ ID NO: 50 is the determined 5' cDNA sequence for L86S-12
- 10 SEQ ID NO: 51 is the determined 5' cDNA sequence for L86S-16
  - SEQ ID NO: 52 is the determined 5' cDNA sequence for L86S-25
  - SEQ ID NO: 53 is the determined 5' cDNA sequence for L86S-36
  - SEO ID NO: 54 is the determined 5' cDNA sequence for L86S-40
  - SEQ ID NO: 55 is the determined 5' cDNA sequence for L86S-46
- 15 SEQ ID NO: 56 is the predicted amino acid sequence for L86S-3
  - SEQ ID NO: 57 is the predicted amino acid sequence for L86S-12
  - SEQ ID NO: 58 is the predicted amino acid sequence for L86S-16
  - SEQ ID NO: 59 is the predicted amino acid sequence for L86S-25
  - SEQ ID NO: 60 is the predicted amino acid sequence for L86S-36
- 20 SEQ ID NO: 61 is the predicted amino acid sequence for L86S-40
  - SEQ ID NO: 62 is the predicted amino acid sequence for L86S-46
  - SEQ ID NO: 63 is the determined 5' cDNA sequence for L86S-30
  - SEQ ID NO: 64 is the determined 5' cDNA sequence for L86S-41
  - SEQ ID NO: 65 is the predicted amino acid sequence from the 5' end of LT86-9
- 25 SEQ ID NO: 66 is the determined extended cDNA sequence for LT86-4
  - SEQ ID NO: 67 is the predicted extended amino acid sequence for LT86-4
  - SEQ ID NO: 68 is the determined 5' cDNA sequence for LT86-20
  - SEQ ID NO: 69 is the determined 3' cDNA sequence for LT86-21
  - SEQ ID NO: 70 is the determined 5' cDNA sequence for LT86-22
- 30 SEQ ID NO: 71 is the determined 5' cDNA sequence for LT86-26

- SEQ ID NO: 72 is the determined 5' cDNA sequence for LT86-27
- SEQ ID NO: 73 is the predicted amino acid sequence for LT86-20
- SEQ ID NO: 74 is the predicted amino acid sequence for LT86-21
- SEQ ID NO: 75 is the predicted amino acid sequence for LT86-22
- 5 SEQ ID NO: 76 is the predicted amino acid sequence for LT86-26
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  - SEQ ID NO: 80 is the determined extended cDNA sequence for L86S-46
- 10 SEQ ID NO: 81 is the predicted extended amino acid sequence for L86S-12
  - SEQ ID NO: 82 is the predicted extended amino acid sequence for L86S-36
  - SEQ ID NO: 83 is the predicted extended amino acid sequence for L86S-46
  - SEQ ID NO: 84 is the determined 5'cDNA sequence for L86S-6
  - SEQ ID NO: 85 is the determined 5'cDNA sequence for L86S-11
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  - SEQ ID NO: 87 is the determined 5'cDNA sequence for L86S-29
  - SEQ ID NO: 88 is the determined 5'cDNA sequence for L86S-34
  - SEQ ID NO: 89 is the determined 5'cDNA sequence for L86S-39
  - SEQ ID NO: 90 is the determined 5'cDNA sequence for L86S-47
- 20 SEQ ID NO: 91 is the determined 5'cDNA sequence for L86S-49
  - SEQ ID NO: 92 is the determined 5'cDNA sequence for L86S-51
  - SEQ ID NO: 93 is the predicted amino acid sequence for L86S-6
  - SEQ ID NO: 94 is the predicted amino acid sequence for L86S-11
  - SEQ ID NO: 95 is the predicted amino acid sequence for L86S-14
- 25 SEQ ID NO: 96 is the predicted amino acid sequence for L86S-29
  - SEQ ID NO: 97 is the predicted amino acid sequence for L86S-34
  - SEQ ID NO: 98 is the predicted amino acid sequence for L86S-39
  - SEQ ID NO: 99 is the predicted amino acid sequence for L86S-47
  - SEQ ID NO: 100 is the predicted amino acid sequence for L86S-49
- 30 SEQ ID NO: 101 is the predicted amino acid sequence for L86S-51

- SEQ ID NO: 102 is the determined DNA sequence for SLT-T1 SEQ ID NO: 103 is the determined 5' cDNA sequence for SLT-T2 SEQ ID NO: 104 is the determined 5' cDNA sequence for SLT-T3 SEQ ID NO: 105 is the determined 5' cDNA sequence for SLT-T5 SEQ ID NO: 106 is the determined 5' cDNA sequence for SLT-T7 SEQ ID NO: 107 is the determined 5' cDNA sequence for SLT-T9 SEQ ID NO: 108 is the determined 5' cDNA sequence for SLT-T10 SEO ID NO: 109 is the determined 5' cDNA sequence for SLT-T11 SEQ ID NO: 110 is the determined 5' cDNA sequence for SLT-T12 10 SEQ ID NO: 111 is the predicted amino acid sequence for SLT-T1 SEQ ID NO: 112 is the predicted amino acid sequence for SLT-T2 SEQ ID NO: 113 is the predicted amino acid sequence for SLT-T3 SEO ID NO: 114 is the predicted amino acid sequence for SLT-T10 SEQ ID NO: 115 is the predicted amino acid sequence for SLT-T12 SEQ ID NO: 116 is the determined 5' cDNA sequence for SALT-T3 15 SEQ ID NO: 117 is the determined 5' cDNA sequence for SALT-T4 SEQ ID NO: 118 is the determined 5' cDNA sequence for SALT-T7 SEQ ID NO: 119 is the determined 5' cDNA sequence for SALT-T8 SEQ ID NO: 120 is the determined 5' cDNA sequence for SALT-T9 20 SEQ ID NO: 121 is the predicted amino acid sequence for SALT-T3 SEO ID NO: 122 is the predicted amino acid sequence for SALT-T4 SEQ ID NO: 123 is the predicted amino acid sequence for SALT-T7 SEQ ID NO: 124 is the predicted amino acid sequence for SALT-T8 SEO ID NO: 125 is the predicted amino acid sequence for SALT-T9 25 SEQ ID NO: 126 is the determined cDNA sequence for PSLT-1 SEQ ID NO: 127 is the determined cDNA sequence for PSLT-2 SEQ ID NO: 128 is the determined cDNA sequence for PSLT-7 SEQ ID NO: 129 is the determined cDNA sequence for PSLT-13
- 30 SEQ ID NO: 131 is the determined cDNA sequence for PSLT-28

SEQ ID NO: 130 is the determined cDNA sequence for PSLT-27

SEQ ID NO: 132 is the determined cDNA sequence for PSLT-30 SEQ ID NO: 133 is the determined cDNA sequence for PSLT-40 SEQ ID NO: 134 is the determined cDNA sequence for PSLT-69 SEO ID NO: 135 is the determined cDNA sequence for PSLT-71 SEQ ID NO: 136 is the determined cDNA sequence for PSLT-73 5 SEQ ID NO: 137 is the determined cDNA sequence for PSLT-79 SEO ID NO: 138 is the determined cDNA sequence for PSLT-03 SEO ID NO: 139 is the determined cDNA sequence for PSLT-09 SEQ ID NO: 140 is the determined cDNA sequence for PSLT-011 SEQ ID NO: 141 is the determined cDNA sequence for PSLT-041 10 SEO ID NO: 142 is the determined cDNA sequence for PSLT-62 SEQ ID NO: 143 is the determined cDNA sequence for PSLT-6 SEQ ID NO: 144 is the determined cDNA sequence for PSLT-37 SEQ ID NO: 145 is the determined cDNA sequence for PSLT-74 SEQ ID NO: 146 is the determined cDNA sequence for PSLT-010 15 SEQ ID NO: 147 is the determined cDNA sequence for PSLT-012 SEQ ID NO: 148 is the determined cDNA sequence for PSLT-037 SEO ID NO: 149 is the determined 5' cDNA sequence for SAL-3 SEQ ID NO: 150 is the determined 5' cDNA sequence for SAL-24 20 SEQ ID NO: 151 is the determined 5' cDNA sequence for SAL-25 SEQ ID NO: 152 is the determined 5' cDNA sequence for SAL-33 SEQ ID NO: 153 is the determined 5' cDNA sequence for SAL-50 SEQ ID NO: 154 is the determined 5' cDNA sequence for SAL-57 SEO ID NO: 155 is the determined 5' cDNA sequence for SAL-66 25 SEQ ID NO: 156 is the determined 5' cDNA sequence for SAL-82 SEQ ID NO: 157 is the determined 5' cDNA sequence for SAL-99 SEQ ID NO: 158 is the determined 5' cDNA sequence for SAL-104 SEQ ID NO: 159 is the determined 5' cDNA sequence for SAL-109 SEQ ID NO: 160 is the determined 5' cDNA sequence for SAL-5

SEQ ID NO: 161 is the determined 5' cDNA sequence for SAL-8

- SEQ ID NO: 162 is the determined 5' cDNA sequence for SAL-12 SEQ ID NO: 163 is the determined 5' cDNA sequence for SAL-14 SEQ ID NO: 164 is the determined 5' cDNA sequence for SAL-16 SEQ ID NO: 165 is the determined 5' cDNA sequence for SAL-23 SEQ ID NO: 166 is the determined 5' cDNA sequence for SAL-26 SEQ ID NO: 167 is the determined 5' cDNA sequence for SAL-29 SEQ ID NO: 168 is the determined 5' cDNA sequence for SAL-32 SEQ ID NO: 169 is the determined 5' cDNA sequence for SAL-39 SEQ ID NO: 170 is the determined 5' cDNA sequence for SAL-42 10 SEQ ID NO: 171 is the determined 5' cDNA sequence for SAL-43 SEO ID NO: 172 is the determined 5' cDNA sequence for SAL-44 SEQ ID NO: 173 is the determined 5' cDNA sequence for SAL-48 SEQ ID NO: 174 is the determined 5' cDNA sequence for SAL-68 SEQ ID NO: 175 is the determined 5' cDNA sequence for SAL-72 15 SEQ ID NO: 176 is the determined 5' cDNA sequence for SAL-77 SEQ ID NO: 177 is the determined 5' cDNA sequence for SAL-86 SEQ ID NO: 178 is the determined 5' cDNA sequence for SAL-88 SEQ ID NO: 179 is the determined 5' cDNA sequence for SAL-93 SEQ ID NO: 180 is the determined 5' cDNA sequence for SAL-100 20 SEQ ID NO: 181 is the determined 5' cDNA sequence for SAL-105 SEQ ID NO: 182 is the predicted amino acid sequence for SAL-3 SEQ ID NO: 183 is the predicted amino acid sequence for SAL-24 SEQ ID NO: 184 is a first predicted amino acid sequence for SAL-25 SEQ ID NO: 185 is a second predicted amino acid sequence for SAL-25 25 SEQ ID NO: 186 is the predicted amino acid sequence for SAL-33 SEQ ID NO: 187 is a first predicted amino acid sequence for SAL-50 SEQ ID NO: 188 is the predicted amino acid sequence for SAL-57 SEQ ID NO: 189 is a first predicted amino acid sequence for SAL-66
- 30 SEQ ID NO: 191 is the predicted amino acid sequence for SAL-82

SEQ ID NO: 190 is a second predicted amino acid sequence for SAL-66

- SEQ ID NO: 192 is the predicted amino acid sequence for SAL-99 SEQ ID NO: 193 is the predicted amino acid sequence for SAL-104 SEQ ID NO: 194 is the predicted amino acid sequence for SAL-5 SEO ID NO: 195 is the predicted amino acid sequence for SAL-8 SEO ID NO: 196 is the predicted amino acid sequence for SAL-12 SEQ ID NO: 197 is the predicted amino acid sequence for SAL-14 SEQ ID NO: 198 is the predicted amino acid sequence for SAL-16 SEO ID NO: 199 is the predicted amino acid sequence for SAL-23 SEQ ID NO: 200 is the predicted amino acid sequence for SAL-26 10 SEQ ID NO: 201 is the predicted amino acid sequence for SAL-29 SEQ ID NO: 202 is the predicted amino acid sequence for SAL-32 SEQ ID NO: 203 is the predicted amino acid sequence for SAL-39 SEQ ID NO: 204 is the predicted amino acid sequence for SAL-42 SEQ ID NO: 205 is the predicted amino acid sequence for SAL-43 SEQ ID NO: 206 is the predicted amino acid sequence for SAL-44 15 SEQ ID NO: 207 is the predicted amino acid sequence for SAL-48 SEQ ID NO: 208 is the predicted amino acid sequence for SAL-68 SEQ ID NO: 209 is the predicted amino acid sequence for SAL-72 SEQ ID NO: 210 is the predicted amino acid sequence for SAL-77 SEQ ID NO: 211 is the predicted amino acid sequence for SAL-86 20 SEQ ID NO: 212 is the predicted amino acid sequence for SAL-88 SEQ ID NO: 213 is the predicted amino acid sequence for SAL-93 SEQ ID NO: 214 is the predicted amino acid sequence for SAL-100 SEQ ID NO: 215 is the predicted amino acid sequence for SAL-105 25 SEO ID NO: 216 is a second predicted amino acid sequence for SAL-50 SEQ ID NO: 217 is the determined cDNA sequence for SSLT-4 SEQ ID NO: 218 is the determined cDNA sequence for SSLT-9
- SEQ ID NO: 220 is the determined cDNA sequence for SSLT-12
  30 SEQ ID NO: 221 is the determined cDNA sequence for SSLT-19

SEQ ID NO: 219 is the determined cDNA sequence for SSLT-10

SEQ ID NO: 222 is the determined cDNA sequence for SSLT-31 SEQ ID NO: 223 is the determined cDNA sequence for SSLT-38 SEQ ID NO: 224 is the determined cDNA sequence for LT4690-2 SEQ ID NO: 225 is the determined cDNA sequence for LT4690-3 SEQ ID NO: 226 is the determined cDNA sequence for LT4690-22 SEQ ID NO: 227 is the determined cDNA sequence for LT4690-24 SEQ ID NO: 228 is the determined cDNA sequence for LT4690-37 SEO ID NO: 229 is the determined cDNA sequence for LT4690-39 SEQ ID NO: 230 is the determined cDNA sequence for LT4690-40 10 SEQ ID NO: 231 is the determined cDNA sequence for LT4690-41 SEO ID NO: 232 is the determined cDNA sequence for LT4690-49 SEQ ID NO: 233 is the determined 3' cDNA sequence for LT4690-55 SEQ ID NO: 234 is the determined 5' cDNA sequence for LT4690-55 SEQ ID NO: 235 is the determined cDNA sequence for LT4690-59 SEQ ID NO: 236 is the determined cDNA sequence for LT4690-63 15 SEQ ID NO: 237 is the determined cDNA sequence for LT4690-71 SEQ ID NO: 238 is the determined cDNA sequence for 2LT-3 SEQ ID NO: 239 is the determined cDNA sequence for 2LT-6 SEO ID NO: 240 is the determined cDNA sequence for 2LT-22 SEQ ID NO: 241 is the determined cDNA sequence for 2LT-25 20 SEQ ID NO: 242 is the determined cDNA sequence for 2LT-26 SEQ ID NO: 243 is the determined cDNA sequence for 2LT-31 SEQ ID NO: 244 is the determined cDNA sequence for 2LT-36 SEO ID NO: 245 is the determined cDNA sequence for 2LT-42 25 SEQ ID NO: 246 is the determined cDNA sequence for 2LT-44 SEQ ID NO: 247 is the determined cDNA sequence for 2LT-54 SEO ID NO: 248 is the determined cDNA sequence for 2LT-55 SEQ ID NO: 249 is the determined cDNA sequence for 2LT-57

SEQ ID NO: 250 is the determined cDNA sequence for 2LT-58

SEQ ID NO: 251 is the determined cDNA sequence for 2LT-59

SEQ ID NO: 252 is the determined cDNA sequence for 2LT-62 SEQ ID NO: 253 is the determined cDNA sequence for 2LT-63 SEO ID NO: 254 is the determined cDNA sequence for 2LT-65 SEO ID NO: 255 is the determined cDNA sequence for 2LT-66 SEQ ID NO: 256 is the determined cDNA sequence for 2LT-70 5 SEQ ID NO: 257 is the determined cDNA sequence for 2LT-73 SEQ ID NO: 258 is the determined cDNA sequence for 2LT-74 SEO ID NO: 259 is the determined cDNA sequence for 2LT-76 SEQ ID NO: 260 is the determined cDNA sequence for 2LT-77 10 SEQ ID NO: 261 is the determined cDNA sequence for 2LT-78 SEQ ID NO: 262 is the determined cDNA sequence for 2LT-80 SEO ID NO: 263 is the determined cDNA sequence for 2LT-85 SEQ ID NO: 264 is the determined cDNA sequence for 2LT-87 SEQ ID NO: 265 is the determined cDNA sequence for 2LT-89 SEQ ID NO: 266 is the determined cDNA sequence for 2LT-94 15 SEQ ID NO: 267 is the determined cDNA sequence for 2LT-95 SEO ID NO: 268 is the determined cDNA sequence for 2LT-98 SEQ ID NO: 269 is the determined cDNA sequence for 2LT-100 SEO ID NO: 270 is the determined cDNA sequence for 2LT-103 SEQ ID NO: 271 is the determined cDNA sequence for 2LT-105 20 SEQ ID NO: 272 is the determined cDNA sequence for 2LT-107 SEQ ID NO: 273 is the determined cDNA sequence for 2LT-108 SEQ ID NO: 274 is the determined cDNA sequence for 2LT-109 SEO ID NO: 275 is the determined cDNA sequence for 2LT-118 25 SEQ ID NO: 276 is the determined cDNA sequence for 2LT-120 SEO ID NO: 277 is the determined cDNA sequence for 2LT-121 SEQ ID NO: 278 is the determined cDNA sequence for 2LT-122 SEQ ID NO: 279 is the determined cDNA sequence for 2LT-124 SEQ ID NO: 280 is the determined cDNA sequence for 2LT-126

SEQ ID NO: 281 is the determined cDNA sequence for 2LT-127

- SEQ ID NO: 282 is the determined cDNA sequence for 2LT-128
- SEQ ID NO: 283 is the determined cDNA sequence for 2LT-129
- SEQ ID NO: 284 is the determined cDNA sequence for 2LT-133
- SEQ ID NO: 285 is the determined cDNA sequence for 2LT-137
- 5 SEQ ID NO: 286 is the determined cDNA sequence for LT4690-71
  - SEQ ID NO: 287 is the determined cDNA sequence for LT4690-82
  - SEQ ID NO: 288 is the determined full-length cDNA sequence for SSLT-74
  - SEQ ID NO: 289 is the determined cDNA sequence for SSLT-78
  - SEQ ID NO: 290 is the determined cDNA sequence for SCC1-8.
- 10 SEQ ID NO: 291 is the determined cDNA sequence for SCC1-12.
  - SEQ ID NO: 292 is the determined cDNA sequence for SCC1-336
    - SEQ ID NO: 293 is the determined cDNA sequence for SCC1-344
    - SEQ ID NO: 294 is the determined cDNA sequence for SCC1-345
    - SEQ ID NO: 295 is the determined cDNA sequence for SCC1-346
- 15 SEQ ID NO: 296 is the determined cDNA sequence for SCC1-348
  - SEQ ID NO: 297 is the determined cDNA sequence for SCC1-350
  - SEQ ID NO: 298 is the determined cDNA sequence for SCC1-352
  - SEQ ID NO: 299 is the determined cDNA sequence for SCC1-354
  - SEQ ID NO: 300 is the determined cDNA sequence for SCC1-355
- 20 SEO ID NO: 301 is the determined cDNA sequence for SCC1-356
  - SEQ ID NO: 302 is the determined cDNA sequence for SCC1-357
  - SEQ ID NO: 303 is the determined cDNA sequence for SCC1-501
  - SEQ ID NO: 304 is the determined cDNA sequence for SCC1-503
  - SEQ ID NO: 305 is the determined cDNA sequence for SCC1-513
- 25 SEQ ID NO: 306 is the determined cDNA sequence for SCC1-516
  - SEQ ID NO: 307 is the determined cDNA sequence for SCC1-518
  - SEQ ID NO: 308 is the determined cDNA sequence for SCC1-519
  - SEQ ID NO: 309 is the determined cDNA sequence for SCC1-522
  - SEQ ID NO: 310 is the determined cDNA sequence for SCC1-523
- 30 SEQ ID NO: 311 is the determined cDNA sequence for SCC1-525

SEQ ID NO: 312 is the determined cDNA sequence for SCC1-527 SEQ ID NO: 313 is the determined cDNA sequence for SCC1-529 SEO ID NO: 314 is the determined cDNA sequence for SCC1-530 SEQ ID NO: 315 is the determined cDNA sequence for SCC1-531 5 SEO ID NO: 316 is the determined cDNA sequence for SCC1-532 SEQ ID NO: 317 is the determined cDNA sequence for SCC1-533 SEO ID NO: 318 is the determined cDNA sequence for SCC1-536 SEQ ID NO: 319 is the determined cDNA sequence for SCC1-538 SEQ ID NO: 320 is the determined cDNA sequence for SCC1-539 SEQ ID NO: 321 is the determined cDNA sequence for SCC1-541 10 SEQ ID NO: 322 is the determined cDNA sequence for SCC1-542 SEO ID NO: 323 is the determined cDNA sequence for SCC1-546 SEQ ID NO: 324 is the determined cDNA sequence for SCC1-549 SEQ ID NO: 325 is the determined cDNA sequence for SCC1-551 15 SEO ID NO: 326 is the determined cDNA sequence for SCC1-552 SEO ID NO: 327 is the determined cDNA sequence for SCC1-554 SEQ ID NO: 328 is the determined cDNA sequence for SCC1-558 SEQ ID NO: 329 is the determined cDNA sequence for SCC1-559 SEQ ID NO: 330 is the determined cDNA sequence for SCC1-561 SEO ID NO: 331 is the determined cDNA sequence for SCC1-562 20 SEQ ID NO: 332 is the determined cDNA sequence for SCC1-564 SEQ ID NO: 333 is the determined cDNA sequence for SCC1-565 SEQ ID NO: 334 is the determined cDNA sequence for SCC1-566 SEQ ID NO: 335 is the determined cDNA sequence for SCC1-567 25 SEQ ID NO: 336 is the determined cDNA sequence for SCC1-568 SEQ ID NO: 337 is the determined cDNA sequence for SCC1-570 SEQ ID NO: 338 is the determined cDNA sequence for SCC1-572 SEQ ID NO: 339 is the determined cDNA sequence for SCC1-575 SEQ ID NO: 340 is the determined cDNA sequence for SCC1-576 30 SEQ ID NO: 341 is the determined cDNA sequence for SCC1-577

SEQ ID NO: 342 is the determined cDNA sequence for SCC1-578 SEQ ID NO: 343 is the determined cDNA sequence for SCC1-582 SEO ID NO: 344 is the determined cDNA sequence for SCC1-583 SEQ ID NO: 345 is the determined cDNA sequence for SCC1-586 SEQ ID NO: 346 is the determined cDNA sequence for SCC1-588 SEO ID NO: 347 is the determined cDNA sequence for SCC1-590 SEQ ID NO: 348 is the determined cDNA sequence for SCC1-591 SEO ID NO: 349 is the determined cDNA sequence for SCC1-592 SEQ ID NO: 350 is the determined cDNA sequence for SCC1-593 SEO ID NO: 351 is the determined cDNA sequence for SCC1-594 10 SEQ ID NO: 352 is the determined cDNA sequence for SCC1-595 SEO ID NO: 353 is the determined cDNA sequence for SCC1-596 SEO ID NO: 354 is the determined cDNA sequence for SCC1-598 SEQ ID NO: 355 is the determined cDNA sequence for SCC1-599 15 SEO ID NO: 356 is the determined cDNA sequence for SCC1-602 SEO ID NO: 357 is the determined cDNA sequence for SCC1-604 SEQ ID NO: 358 is the determined cDNA sequence for SCC1-605 SEQ ID NO: 359 is the determined cDNA sequence for SCC1-606 SEQ ID NO: 360 is the determined cDNA sequence for SCC1-607 SEO ID NO: 361 is the determined cDNA sequence for SCC1-608 20 SEQ ID NO: 362 is the determined cDNA sequence for SCC1-610 SEO ID NO: 363 is the determined cDNA sequence for clone DMS79T1 SEQ ID NO: 364 is the determined cDNA sequence for clone DMS79T2 SEQ ID NO: 365 is the determined cDNA sequence for clone DMS79T3 25 SEQ ID NO: 366 is the determined cDNA sequence for clone DMS79T5 SEQ ID NO: 367 is the determined cDNA sequence for clone DMS79T6 SEQ ID NO: 368 is the determined cDNA sequence for clone DMS79T7 SEQ ID NO: 369 is the determined cDNA sequence for clone DMS79T9 SEQ ID NO: 370 is the determined cDNA sequence for clone DMS79T10

SEQ ID NO: 371 is the determined cDNA sequence for clone DMS79T11

- SEQ ID NO: 372 is the determined cDNA sequence for clone 128T1
- SEO ID NO: 373 is the determined cDNA sequence for clone 128T2
- SEQ ID NO: 374 is the determined cDNA sequence for clone 128T3
- SEO ID NO: 375 is the determined cDNA sequence for clone 128T4
- 5 SEQ ID NO: 376 is the determined cDNA sequence for clone 128T5
  - SEQ ID NO: 377 is the determined cDNA sequence for clone 128T7
  - SEQ ID NO: 378 is the determined cDNA sequence for clone 128T9
  - SEO ID NO: 379 is the determined cDNA sequence for clone 128T10
  - SEQ ID NO: 380 is the determined cDNA sequence for clone 128T11
- 10 SEQ ID NO: 381 is the determined cDNA sequence for clone 128T12
  - SEO ID NO: 382 is the determined cDNA sequence for clone NCIH69T3
  - SEQ ID NO: 383 is the determined cDNA sequence for clone NCIH69T5
  - SEQ ID NO: 384 is the determined cDNA sequence for clone NCIH69T6
  - SEQ ID NO: 385 is the determined cDNA sequence for clone NCIH69T7
- 15 SEQ ID NO: 386 is the determined cDNA sequence for clone NCIH69T9
  - SEQ ID NO: 387 is the determined cDNA sequence for clone NCIH69T10
  - SEQ ID NO: 388 is the determined cDNA sequence for clone NCIH69T11
  - SEQ ID NO: 389 is the determined cDNA sequence for clone NCIH69T12
  - SEQ ID NO: 390 is the full-length cDNA sequence for 128T1
- 20 SEO ID NO: 391 is the amino acid sequence for 128T1
  - SEQ ID NO: 392 is the full-length cDNA sequence for 2LT-128
  - SEQ ID NO: 393 is the amino acid sequence for 2LT-128
  - SEQ ID NO: 394 is an extended cDNA sequence for clone SCC1-542
  - SEO ID NO: 395 is the amino acid sequence corresponding to SEQ ID NO:394
- 25 SEQ ID NO: 396 is an extended cDNA sequence for clone SCC1-593
  - SEQ ID NO: 397 is the amino acid sequence corresponding to SEQ ID NO:396
  - SEO ID NO:398 is the determined cDNA sequence for 55508.1
  - SEO ID NO:399 is the determined cDNA sequence for 55509.1
  - SEQ ID NO:400 is the determined cDNA sequence for 54243.1
- 30 SEQ ID NO:401 is the determined cDNA sequence for 54251.1

- SEQ ID NO:402 is the determined cDNA sequence for 54252.1
- SEQ ID NO:403 is the determined cDNA sequence for 54253.1
- SEQ ID NO:404 is the determined cDNA sequence for 55518.1
- SEQ ID NO:405 is the determined cDNA sequence for 54258.1
- 5 SEQ ID NO:406 is the determined cDNA sequence for 54575.1
  - SEQ ID NO:407 is the determined cDNA sequence for 54577.1
  - SEQ ID NO:408 is the determined cDNA sequence for 54584.1
  - SEQ ID NO:409 is the determined cDNA sequence for 55521.1
  - SEO ID NO:410 is the determined cDNA sequence for 54589.1
- 10 SEQ ID NO:411 is the determined cDNA sequence for 54592.1
  - SEQ ID NO:412 is the determined cDNA sequence for 55134.1
  - SEQ ID NO:413 is the determined cDNA sequence for 55137.1
  - SEQ ID NO:414 is the determined cDNA sequence for 55140.1
  - SEQ ID NO:415 is the determined cDNA sequence for 55531.1
- 15 SEQ ID NO:416 is the determined cDNA sequence for 55532.1
  - SEQ ID NO:417 is the determined cDNA sequence for 54621.1
  - SEQ ID NO:418 is the determined cDNA sequence for 55548.1
  - SEQ ID NO:419 is the determined cDNA sequence for 54623.1
  - SEQ ID NO:420 is the determined cDNA sequence for L39
- 20 SEQ ID NO:421 is the predicted amino acid sequence for L39
  - SEQ ID NO:422 is the determined cDNA sequence for SCC2-29
  - SEQ ID NO:423 is the determined cDNA sequence for SCC2-36
  - SEQ ID NO:424 is the determined cDNA sequence for SCC2-60
  - SEO ID NO:425 is the predicted amino acid sequence for SCC2-29
- 25 SEQ ID NO:426 is the predicted amino acid sequence for SCC2-36
  - SEQ ID NO:427 is the predicted amino acid sequence for SCC2-60
  - SEQ ID NO:428 is an extended cDNA sequence for the clone 20129, also referred to as 2LT-3, set forth in SEQ ID NO: 238
  - SEQ ID NO:429 is an extended cDNA sequence for the clone 20347, also referred to as 2LT-26, set forth in SEQ ID NO: 242

- SEQ ID NO:430 is an extended cDNA sequence for the clone 21282, also referred to as 2LT-57, set forth in SEQ ID NO: 249
- SEQ ID NO:431 is an extended cDNA sequence for the clone 21283, also referred to as 2LT-58, set forth in SEQ ID NO: 250
- 5 SEQ ID NO:432 is an extended cDNA sequence for the clone 21484, also referred to as 2LT-98, set forth in SEQ ID NO: 268
  - SEQ ID NO:433 is an extended cDNA sequence for the clone 21871, also referred to as 2LT-124, set forth in SEQ ID NO: 279
  - SEQ ID NO:434 is an amino acid sequence encoded by SEQ ID NO: 428
- 10 SEQ ID NO:435 is an amino acid sequence encoded by SEQ ID NO: 429
  - SEQ ID NO:436 is an amino acid sequence encoded by SEQ ID NO: 430
  - SEO ID NO:437 is an amino acid sequence encoded by SEQ ID NO: 431
  - SEQ ID NO:438 is an amino acid sequence encoded by SEQ ID NO: 432
  - SEQ ID NO:439 is an amino acid sequence encoded by SEQ ID NO: 433
- 15 SEQ ID NO:440 is the determined cDNA sequence for clone 19A4

## DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to compositions and methods for using the compositions, for example in the therapy and diagnosis of cancer, such as lung cancer. Certain illustrative compositions described herein include lung tumor polypeptides, polynucleotides encoding such polypeptides, binding agents such as antibodies, antigen presenting cells (APCs) and/or immune system cells (e.g., T cells). A "lung tumor protein," as the term is used herein, refers generally to a protein that is expressed in lung tumor cells at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in a normal tissue, as determined using a representative assay provided herein. Certain lung tumor proteins are tumor proteins that

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react detectably (within an immunoassay, such as an ELISA or Western blot) with antisera of a patient afflicted with lung cancer.

Therefore, in accordance with the above, and as described further below, the present invention provides illustrative polynucleotide compositions having sequences set forth in SEQ ID NOs:217-390, 392, 394, 396, 398-420, 422-424, 428-433 and 440 illustrative polypeptide compositions having amino acid sequences set forth in SEQ ID NOs:391, 393, 395 and 397, 421, 425-427 and 434-439, antibody compositions capable of binding such polypeptides, and numerous additional embodiments employing such compositions, for example in the detection, diagnosis and/or therapy of human lung cancer.

#### 10 POLYNUCLEOTIDE COMPOSITIONS

As used herein, the terms "DNA segment" and "polynucleotide" refer to a DNA molecule that has been isolated free of total genomic DNA of a particular species. Therefore, a DNA segment encoding a polypeptide refers to a DNA segment that contains one or more coding sequences yet is substantially isolated away from, or purified free from, total genomic DNA of the species from which the DNA segment is obtained. Included within the terms "DNA segment" and "polynucleotide" are DNA segments and smaller fragments of such segments, and also recombinant vectors, including, for example, plasmids, cosmids, phagemids, phage, viruses, and the like.

As will be understood by those skilled in the art, the DNA segments of this invention can include genomic sequences, extra-genomic and plasmid-encoded sequences and smaller engineered gene segments that express, or may be adapted to express, proteins, polypeptides, peptides and the like. Such segments may be naturally isolated, or modified synthetically by the hand of man.

"Isolated," as used herein, means that a polynucleotide is substantially away
from other coding sequences, and that the DNA segment does not contain large portions of
unrelated coding DNA, such as large chromosomal fragments or other functional genes or
polypeptide coding regions. Of course, this refers to the DNA segment as originally

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isolated, and does not exclude genes or coding regions later added to the segment by the hand of man.

As will be recognized by the skilled artisan, polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (*i.e.*, an endogenous sequence that encodes a lung tumor protein or a portion thereof) or may comprise a variant, or a biological or antigenic functional equivalent of such a sequence. Polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions, as further described below, preferably such that the immunogenicity of the encoded polypeptide is not diminished, relative to a native tumor protein. The effect on the immunogenicity of the encoded polypeptide may generally be assessed as described herein. The term "variants" also encompasses homologous genes of xenogenic origin.

When comparing polynucleotide or polypeptide sequences, two sequences are said to be "identical" if the sequence of nucleotides or amino acids in the two sequences is the same when aligned for maximum correspondence, as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment

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schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenes pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS* 5:151-153; Myers, E.W. and Muller W. (1988) *CABIOS* 4:11-17; Robinson, E.D. (1971) *Comb. Theor* 11:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol.* 4:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy* – the Principles and Practice of Numerical Taxonomy, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad., Sci. USA* 80:726-730.

Alternatively, optimal alignment of sequences for comparison may be conducted by the local identity algorithm of Smith and Waterman (1981) *Add. APL. Math* 2:482, by the identity alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity methods of Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85: 2444, by computerized implementations of these algorithms (GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by inspection.

One preferred example of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul *et al.* (1977) *Nucl. Acids Res.* 25:3389-3402 and Altschul *et al.* (1990) *J. Mol. Biol.* 215:403-410, respectively. BLAST and BLAST 2.0 can be used, for example with the parameters described herein, to determine percent sequence identity for the polynucleotides and polypeptides of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. In one illustrative example, cumulative scores can be calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always >0) and N (penalty score for mismatching residues; always <0). For amino acid sequences, a scoring matrix can be used to calculate the cumulative score.

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Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, and expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff and Henikoff (1989) *Proc. Natl. Acad. Sci. USA* 89:10915) alignments, (B) of 50, expectation (E) of 10, M=5, N=-4 and a comparison of both strands.

Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide or polypeptide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.*, the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Therefore, the present invention encompasses polynucleotide and polypeptide sequences having substantial identity to the sequences disclosed herein, for example those comprising at least 50% sequence identity, preferably at least 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% or higher, sequence identity compared to a polynucleotide or polypeptide sequence of this invention using the methods described herein, (e.g., BLAST analysis using standard parameters, as described below). One skilled in this art will recognize that these values can be appropriately adjusted to determine corresponding identity of proteins encoded by two nucleotide

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sequences by taking into account codon degeneracy, amino acid similarity, reading frame positioning and the like.

In additional embodiments, the present invention provides isolated polynucleotides and polypeptides comprising various lengths of contiguous stretches of sequence identical to or complementary to one or more of the sequences disclosed herein. For example, polynucleotides are provided by this invention that comprise at least about 15, 20, 30, 40, 50, 75, 100, 150, 200, 300, 400, 500 or 1000 or more contiguous nucleotides of one or more of the sequences disclosed herein as well as all intermediate lengths there between. It will be readily understood that "intermediate lengths", in this context, means any length between the quoted values, such as 16, 17, 18, 19, etc.; 21, 22, 23, etc.; 30, 31, 32, etc.; 50, 51, 52, 53, etc.; 100, 101, 102, 103, etc.; 150, 151, 152, 153, etc.; including all integers through 200-500; 500-1,000, and the like.

The polynucleotides of the present invention, or fragments thereof, regardless of the length of the coding sequence itself, may be combined with other DNA sequences, such as promoters, polyadenylation signals, additional restriction enzyme sites, multiple cloning sites, other coding segments, and the like, such that their overall length may vary considerably. It is therefore contemplated that a nucleic acid fragment of almost any length may be employed, with the total length preferably being limited by the ease of preparation and use in the intended recombinant DNA protocol. For example, illustrative DNA segments with total lengths of about 10,000, about 5000, about 3000, about 2,000, about 1,000, about 500, about 200, about 50 base pairs in length, and the like, (including all intermediate lengths) are contemplated to be useful in many implementations of this invention.

In other embodiments, the present invention is directed to polynucleotides that are capable of hybridizing under moderately stringent conditions to a polynucleotide sequence provided herein, or a fragment thereof, or a complementary sequence thereof. Hybridization techniques are well known in the art of molecular biology. For purposes of illustration, suitable moderately stringent conditions for testing the hybridization of a polynucleotide of this invention with other polynucleotides include prewashing in a

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solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5 X SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS.

Moreover, it will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

#### 15 PROBES AND PRIMERS

In other embodiments of the present invention, the polynucleotide sequences provided herein can be advantageously used as probes or primers for nucleic acid hybridization. As such, it is contemplated that nucleic acid segments that comprise a sequence region of at least about 15 nucleotide long contiguous sequence that has the same sequence as, or is complementary to, a 15 nucleotide long contiguous sequence disclosed herein will find particular utility. Longer contiguous identical or complementary sequences, *e.g.*, those of about 20, 30, 40, 50, 100, 200, 500, 1000 (including all intermediate lengths) and even up to full length sequences will also be of use in certain embodiments.

The ability of such nucleic acid probes to specifically hybridize to a sequence of interest will enable them to be of use in detecting the presence of complementary sequences in a given sample. However, other uses are also envisioned,

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such as the use of the sequence information for the preparation of mutant species primers, or primers for use in preparing other genetic constructions.

Polynucleotide molecules having sequence regions consisting of contiguous nucleotide stretches of 10-14, 15-20, 30, 50, or even of 100-200 nucleotides or so (including intermediate lengths as well), identical or complementary to a polynucleotide sequence disclosed herein, are particularly contemplated as hybridization probes for use in, e.g., Southern and Northern blotting. This would allow a gene product, or fragment thereof, to be analyzed, both in diverse cell types and also in various bacterial cells. The total size of fragment, as well as the size of the complementary stretch(es), will ultimately depend on the intended use or application of the particular nucleic acid segment. Smaller fragments will generally find use in hybridization embodiments, wherein the length of the contiguous complementary region may be varied, such as between about 15 and about 100 nucleotides, but larger contiguous complementarity stretches may be used, according to the length complementary sequences one wishes to detect.

The use of a hybridization probe of about 15-25 nucleotides in length allows the formation of a duplex molecule that is both stable and selective. Molecules having contiguous complementary sequences over stretches greater than 15 bases in length are generally preferred, though, in order to increase stability and selectivity of the hybrid, and thereby improve the quality and degree of specific hybrid molecules obtained. One will generally prefer to design nucleic acid molecules having gene-complementary stretches of 15 to 25 contiguous nucleotides, or even longer where desired.

Hybridization probes may be selected from any portion of any of the sequences disclosed herein. All that is required is to review the sequence set forth in SEQ ID NOs:217-390, 392, 394, 396, 398-420, 422-424, 428-433 and 440, or to any continuous portion of the sequence, from about 15-25 nucleotides in length up to and including the full length sequence, that one wishes to utilize as a probe or primer. The choice of probe and primer sequences may be governed by various factors. For example, one may wish to employ primers from towards the termini of the total sequence.

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Small polynucleotide segments or fragments may be readily prepared by, for example, directly synthesizing the fragment by chemical means, as is commonly practiced using an automated oligonucleotide synthesizer. Also, fragments may be obtained by application of nucleic acid reproduction technology, such as the PCR<sup>TM</sup> technology of U. S. Patent 4,683,202 (incorporated herein by reference), by introducing selected sequences into recombinant vectors for recombinant production, and by other recombinant DNA techniques generally known to those of skill in the art of molecular biology.

The nucleotide sequences of the invention may be used for their ability to selectively form duplex molecules with complementary stretches of the entire gene or gene fragments of interest. Depending on the application envisioned, one will typically desire to employ varying conditions of hybridization to achieve varying degrees of selectivity of probe towards target sequence. For applications requiring high selectivity, one will typically desire to employ relatively stringent conditions to form the hybrids, *e.g.*, one will select relatively low salt and/or high temperature conditions, such as provided by a salt concentration of from about 0.02 M to about 0.15 M salt at temperatures of from about 50°C to about 70°C. Such selective conditions tolerate little, if any, mismatch between the probe and the template or target strand, and would be particularly suitable for isolating related sequences.

Of course, for some applications, for example, where one desires to prepare mutants employing a mutant primer strand hybridized to an underlying template, less stringent (reduced stringency) hybridization conditions will typically be needed in order to allow formation of the heteroduplex. In these circumstances, one may desire to employ salt conditions such as those of from about 0.15 M to about 0.9 M salt, at temperatures ranging from about 20°C to about 55°C. Cross-hybridizing species can thereby be readily identified as positively hybridizing signals with respect to control hybridizations. In any case, it is generally appreciated that conditions can be rendered more stringent by the addition of increasing amounts of formamide, which serves to destabilize the hybrid duplex in the same manner as increased temperature. Thus, hybridization conditions can be

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readily manipulated, and thus will generally be a method of choice depending on the desired results.

#### POLYNUCLEOTIDE IDENTIFICATION AND CHARACTERIZATION

Polynucleotides may be identified, prepared and/or manipulated using any of a variety of well established techniques. For example, a polynucleotide may be identified, as described in more detail below, by screening a microarray of cDNAs for tumor-associated expression (*i.e.*, expression that is at least two fold greater in a tumor than in normal tissue, as determined using a representative assay provided herein). Such screens may be performed, for example, using a Synteni microarray (Palo Alto, CA) according to the manufacturer's instructions (and essentially as described by Schena *et al.*, *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller *et al.*, *Proc. Natl. Acad. Sci. USA 94*:2150-2155, 1997). Alternatively, polynucleotides may be amplified from cDNA prepared from cells expressing the proteins described herein, such as lung tumor cells. Such polynucleotides may be amplified via polymerase chain reaction (PCR). For this approach, sequence-specific primers may be designed based on the sequences provided herein, and may be purchased or synthesized.

An amplified portion of a polynucleotide of the present invention may be used to isolate a full length gene from a suitable library (e.g., a lung tumor cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide probes or primers suitable for amplification. Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (e.g., by nick-translation or end-labeling with <sup>32</sup>P) using well known techniques. A bacterial or bacteriophage library is then generally screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (see Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor

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Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences can then assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, there are numerous amplification techniques for obtaining a full length coding sequence from a partial cDNA sequence. Within such techniques, amplification is generally performed via PCR. Any of a variety of commercially available kits may be used to perform the amplification step. Primers may be designed using, for example, software well known in the art. Primers are preferably 22-30 nucleotides in length, have a GC content of at least 50% and anneal to the target sequence at temperatures of about 68°C to 72°C. The amplified region may be sequenced as described above, and overlapping sequences assembled into a contiguous sequence.

One such amplification technique is inverse PCR (see Triglia et al., Nucl. Acids Res. 16:8186, 1988), which uses restriction enzymes to generate a fragment in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a known region. The amplified sequences are typically subjected to a second round of amplification with the same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Another such technique is known as "rapid amplification of cDNA ends" or RACE. This technique involves the use of an internal primer and an external primer, which hybridizes to a polyA region or vector

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sequence, to identify sequences that are 5' and 3' of a known sequence. Additional techniques include capture PCR (Lagerstrom *et al.*, *PCR Methods Applic. 1*:111-19, 1991) and walking PCR (Parker *et al.*, *Nucl. Acids. Res. 19*:3055-60, 1991). Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (e.g., NCBI BLAST searches), and such ESTs may be used to generate a contiguous full length sequence. Full length DNA sequences may also be obtained by analysis of genomic fragments.

#### POLYNUCLEOTIDE EXPRESSION IN HOST CELLS

In other embodiments of the invention, polynucleotide sequences or fragments thereof which encode polypeptides of the invention, or fusion proteins or functional equivalents thereof, may be used in recombinant DNA molecules to direct expression of a polypeptide in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences that encode substantially the same or a functionally equivalent amino acid sequence may be produced and these sequences may be used to clone and express a given polypeptide.

As will be understood by those of skill in the art, it may be advantageous in some instances to produce polypeptide-encoding nucleotide sequences possessing non-naturally occurring codons. For example, codons preferred by a particular prokaryotic or eukaryotic host can be selected to increase the rate of protein expression or to produce a recombinant RNA transcript having desirable properties, such as a half-life which is longer than that of a transcript generated from the naturally occurring sequence.

Moreover, the polynucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter polypeptide encoding sequences for a variety of reasons, including but not limited to, alterations which modify the cloning, processing, and/or expression of the gene product. For example, DNA

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shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. In addition, site-directed mutagenesis may be used to insert new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, or introduce mutations, and so forth.

In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences may be ligated to a heterologous sequence to encode a fusion protein. For example, to screen peptide libraries for inhibitors of polypeptide activity, it may be useful to encode a chimeric protein that can be recognized by a commercially available antibody. A fusion protein may also be engineered to contain a cleavage site located between the polypeptide-encoding sequence and the heterologous protein sequence, so that the polypeptide may be cleaved and purified away from the heterologous moiety.

Sequences encoding a desired polypeptide may be synthesized, in whole or in part, using chemical methods well known in the art (see Caruthers, M. H. et al. (1980) Nucl. Acids Res. Symp. Ser. 215-223, Horn, T. et al. (1980) Nucl. Acids Res. Symp. Ser. 225-232). Alternatively, the protein itself may be produced using chemical methods to synthesize the amino acid sequence of a polypeptide, or a portion thereof. For example, peptide synthesis can be performed using various solid-phase techniques (Roberge, J. Y. et al. (1995) Science 269:202-204) and automated synthesis may be achieved, for example, using the ABI 431A Peptide Synthesizer (Perkin Elmer, Palo Alto, CA).

A newly synthesized peptide may be substantially purified by preparative high performance liquid chromatography (e.g., Creighton, T. (1983) Proteins, Structures and Molecular Principles, WH Freeman and Co., New York, N.Y.) or other comparable techniques available in the art. The composition of the synthetic peptides may be confirmed by amino acid analysis or sequencing (e.g., the Edman degradation procedure). Additionally, the amino acid sequence of a polypeptide, or any part thereof, may be altered during direct synthesis and/or combined using chemical methods with sequences from other proteins, or any part thereof, to produce a variant polypeptide.

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In order to express a desired polypeptide, the nucleotide sequences encoding the polypeptide, or functional equivalents, may be inserted into appropriate expression vector, *i.e.*, a vector which contains the necessary elements for the transcription and translation of the inserted coding sequence. Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding a polypeptide of interest and appropriate transcriptional and translational control elements. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. Such techniques are described in Sambrook, J. *et al.* (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview, N.Y., and Ausubel, F. M. *et al.* (1989) Current Protocols in Molecular Biology, John Wiley & Sons, New York. N.Y.

A variety of expression vector/host systems may be utilized to contain and express polynucleotide sequences. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with virus expression vectors (e.g., baculovirus); plant cell systems transformed with virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or animal cell systems.

The "control elements" or "regulatory sequences" present in an expression vector are those non-translated regions of the vector--enhancers, promoters, 5' and 3' untranslated regions--which interact with host cellular proteins to carry out transcription and translation. Such elements may vary in their strength and specificity. Depending on the vector system and host utilized, any number of suitable transcription and translation elements, including constitutive and inducible promoters, may be used. For example, when cloning in bacterial systems, inducible promoters such as the hybrid lacZ promoter of the PBLUESCRIPT phagemid (Stratagene, La Jolla, Calif.) or PSPORT1 plasmid (Gibco BRL, Gaithersburg, MD) and the like may be used. In mammalian cell systems, promoters from mammalian genes or from mammalian viruses are generally preferred. If it is necessary to

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generate a cell line that contains multiple copies of the sequence encoding a polypeptide, vectors based on SV40 or EBV may be advantageously used with an appropriate selectable marker.

In bacterial systems, a number of expression vectors may be selected depending upon the use intended for the expressed polypeptide. For example, when large quantities are needed, for example for the induction of antibodies, vectors which direct high level expression of fusion proteins that are readily purified may be used. Such vectors include, but are not limited to, the multifunctional E. coli cloning and expression vectors such as BLUESCRIPT (Stratagene), in which the sequence encoding the polypeptide of interest may be ligated into the vector in frame with sequences for the amino-terminal Met and the subsequent 7 residues of .beta.-galactosidase so that a hybrid protein is produced; pIN vectors (Van Heeke, G. and S. M. Schuster (1989) J. Biol. Chem. 264:5503-5509); and the like, pGEX Vectors (Promega, Madison, Wis.) may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption to glutathione-agarose beads followed by elution in the presence of free glutathione. Proteins made in such systems may be designed to include heparin, thrombin, or factor XA protease cleavage sites so that the cloned polypeptide of interest can be released from the GST moiety at will.

In the yeast, Saccharomyces cerevisiae, a number of vectors containing constitutive or inducible promoters such as alpha factor, alcohol oxidase, and PGH may be used. For reviews, see Ausubel *et al.* (supra) and Grant *et al.* (1987) *Methods Enzymol.* 153:516-544.

In cases where plant expression vectors are used, the expression of sequences encoding polypeptides may be driven by any of a number of promoters. For example, viral promoters such as the 35S and 19S promoters of CaMV may be used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) *EMBO J. 6*:307-311. Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used (Coruzzi, G. *et al.* (1984) *EMBO J. 3*:1671-1680;

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Broglie, R. et al. (1984) Science 224:838-843; and Winter, J. et al. (1991) Results Probl. Cell Differ. 17:85-105). These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. Such techniques are described in a number of generally available reviews (see, for example, Hobbs, S. or Murry, L. E. in McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York, N.Y.; pp. 191-196).

An insect system may also be used to express a polypeptide of interest. For example, in one such system, Autographa californica nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes in Spodoptera frugiperda cells or in Trichoplusia larvae. The sequences encoding the polypeptide may be cloned into a non-essential region of the virus, such as the polyhedrin gene, and placed under control of the polyhedrin promoter. Successful insertion of the polypeptide-encoding sequence will render the polyhedrin gene inactive and produce recombinant virus lacking coat protein. The recombinant viruses may then be used to infect, for example, S. frugiperda cells or Trichoplusia larvae in which the polypeptide of interest may be expressed (Engelhard, E. K. et al. (1994) Proc. Natl. Acad. Sci. 91:3224-3227).

In mammalian host cells, a number of viral-based expression systems are generally available. For example, in cases where an adenovirus is used as an expression vector, sequences encoding a polypeptide of interest may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain a viable virus which is capable of expressing the polypeptide in infected host cells (Logan, J. and Shenk, T. (1984) *Proc. Natl. Acad. Sci. 81*:3655-3659). In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells.

Specific initiation signals may also be used to achieve more efficient translation of sequences encoding a polypeptide of interest. Such signals include the ATG initiation codon and adjacent sequences. In cases where sequences encoding the polypeptide, its initiation codon, and upstream sequences are inserted into the appropriate

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expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a portion thereof, is inserted, exogenous translational control signals including the ATG initiation codon should be provided. Furthermore, the initiation codon should be in the correct reading frame to ensure translation of the entire insert. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers which are appropriate for the particular cell system which is used, such as those described in the literature (Scharf, D. *et al.* (1994) *Results Probl. Cell Differ.* 20:125-162).

In addition, a host cell strain may be chosen for its ability to modulate the expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation. glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" form of the protein may also be used to facilitate correct insertion, folding and/or function. Different host cells such as CHO, HeLa, MDCK, HEK293, and WI38, which have specific cellular machinery and characteristic mechanisms for such post-translational activities, may be chosen to ensure the correct modification and processing of the foreign protein.

For long-term, high-yield production of recombinant proteins, stable expression is generally preferred. For example, cell lines which stably express a polynucleotide of interest may be transformed using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for 1-2 days in an enriched media before they are switched to selective media. The purpose of the selectable marker is to confer resistance to selection, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be proliferated using tissue culture techniques appropriate to the cell type.

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Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase (Wigler, M. et al. (1977) Cell 11:223-32) and adenine phosphoribosyltransferase (Lowy, I. et al. (1990) Cell 22:817-23) genes which can be employed in tk.sup.- or aprt.sup.- cells, respectively. Also, antimetabolite, antibiotic or herbicide resistance can be used as the basis for selection; for example, dhfr which confers resistance to methotrexate (Wigler, M. et al. (1980) Proc. Natl. Acad. Sci. 77:3567-70); npt, which confers resistance to the aminoglycosides, neomycin and G-418 (Colbere-Garapin, F. et al (1981) J. Mol. Biol. 150:1-14); and als or pat, which confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively (Murry, supra). Additional selectable genes have been described, for example, trpB, which allows cells to utilize indole in place of tryptophan, or hisD, which allows cells to utilize histinol in place of histidine (Hartman, S. C. and R. C. Mulligan (1988) Proc. Natl. Acad. Sci. 85:8047-51). Recently, the use of visible markers has gained popularity with such markers as anthocyanins, beta-glucuronidase and its substrate GUS, and luciferase and its substrate luciferin, being widely used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system (Rhodes, C. A. et al. (1995) Methods Mol. Biol. 55:121-131).

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, its presence and expression may need to be confirmed. For example, if the sequence encoding a polypeptide is inserted within a marker gene sequence, recombinant cells containing sequences can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a polypeptide-encoding sequence under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

Alternatively, host cells which contain and express a desired polynucleotide sequence may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations

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and protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein.

A variety of protocols for detecting and measuring the expression of polynucleotide-encoded products, using either polyclonal or monoclonal antibodies specific for the product are known in the art. Examples include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on a given polypeptide may be preferred for some applications, but a competitive binding assay may also be employed. These and other assays are described, among other places, in Hampton, R. *et al.* (1990; Serological Methods, a Laboratory Manual, APS Press, St Paul. Minn.) and Maddox, D. E. *et al.* (1983; *J. Exp. Med. 158*:1211-1216).

A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides include oligolabeling, nick translation, end-labeling or PCR amplification using a labeled nucleotide. Alternatively, the sequences, or any portions thereof may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits. Suitable reporter molecules or labels, which may be used include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with a polynucleotide sequence of interest may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a recombinant cell may be secreted or contained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides of the invention may

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be designed to contain signal sequences which direct secretion of the encoded polypeptide through a prokaryotic or eukaryotic cell membrane. Other recombinant constructions may be used to join sequences encoding a polypeptide of interest to nucleotide sequence encoding a polypeptide domain which will facilitate purification of soluble proteins. Such purification facilitating domains include, but are not limited to, metal chelating peptides such as histidine-tryptophan modules that allow purification on immobilized metals, protein A domains that allow purification on immobilized immunoglobulin, and the domain utilized in the FLAGS extension/affinity purification system (Immunex Corp., Seattle, Wash.). The inclusion of cleavable linker sequences such as those specific for Factor XA or enterokinase (Invitrogen. San Diego, Calif.) between the purification domain and the encoded polypeptide may be used to facilitate purification. One such expression vector provides for expression of a fusion protein containing a polypeptide of interest and a nucleic acid encoding 6 histidine residues preceding a thioredoxin or an enterokinase cleavage site. The histidine residues facilitate purification on IMIAC (immobilized metal ion affinity chromatography) as described in Porath, J. et al. (1992, Prot. Exp. Purif. 3:263-281) while the enterokinase cleavage site provides a means for purifying the desired polypeptide from the fusion protein. A discussion of vectors which contain fusion proteins is provided in Kroll, D. J. et al. (1993; DNA Cell Biol. 12:441-453).

In addition to recombinant production methods, polypeptides of the invention, and fragments thereof, may be produced by direct peptide synthesis using solid-phase techniques (Merrifield J. (1963) *J. Am. Chem. Soc.* 85:2149-2154). Protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be achieved, for example, using Applied Biosystems 431A Peptide Synthesizer (Perkin Elmer). Alternatively, various fragments may be chemically synthesized separately and combined using chemical methods to produce the full length molecule.

#### SITE-SPECIFIC MUTAGENESIS

Site-specific mutagenesis is a technique useful in the preparation of individual peptides, or biologically functional equivalent polypeptides, through specific

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mutagenesis of the underlying polynucleotides that encode them. The technique, well-known to those of skill in the art, further provides a ready ability to prepare and test sequence variants, for example, incorporating one or more of the foregoing considerations, by introducing one or more nucleotide sequence changes into the DNA. Site-specific mutagenesis allows the production of mutants through the use of specific oligonucleotide sequences which encode the DNA sequence of the desired mutation, as well as a sufficient number of adjacent nucleotides, to provide a primer sequence of sufficient size and sequence complexity to form a stable duplex on both sides of the deletion junction being traversed. Mutations may be employed in a selected polynucleotide sequence to improve, alter, decrease, modify, or otherwise change the properties of the polynucleotide itself, and/or alter the properties, activity, composition, stability, or primary sequence of the encoded polypeptide.

In certain embodiments of the present invention, the inventors contemplate the mutagenesis of the disclosed polynucleotide sequences to alter one or more properties of the encoded polypeptide, such as the antigenicity of a polypeptide vaccine. The techniques of site-specific mutagenesis are well-known in the art, and are widely used to create variants of both polypeptides and polynucleotides. For example, site-specific mutagenesis is often used to alter a specific portion of a DNA molecule. In such embodiments, a primer comprising typically about 14 to about 25 nucleotides or so in length is employed, with about 5 to about 10 residues on both sides of the junction of the sequence being altered.

As will be appreciated by those of skill in the art, site-specific mutagenesis techniques have often employed a phage vector that exists in both a single stranded and double stranded form. Typical vectors useful in site-directed mutagenesis include vectors such as the M13 phage. These phage are readily commercially-available and their use is generally well-known to those skilled in the art. Double-stranded plasmids are also routinely employed in site directed mutagenesis that eliminates the step of transferring the gene of interest from a plasmid to a phage.

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In general, site-directed mutagenesis in accordance herewith is performed by first obtaining a single-stranded vector or melting apart of two strands of a double-stranded vector that includes within its sequence a DNA sequence that encodes the desired peptide. An oligonucleotide primer bearing the desired mutated sequence is prepared, generally synthetically. This primer is then annealed with the single-stranded vector, and subjected to DNA polymerizing enzymes such as *E. coli* polymerase I Klenow fragment, in order to complete the synthesis of the mutation-bearing strand. Thus, a heteroduplex is formed wherein one strand encodes the original non-mutated sequence and the second strand bears the desired mutation. This heteroduplex vector is then used to transform appropriate cells, such as *E. coli* cells, and clones are selected which include recombinant vectors bearing the mutated sequence arrangement.

The preparation of sequence variants of the selected peptide-encoding DNA segments using site-directed mutagenesis provides a means of producing potentially useful species and is not meant to be limiting as there are other ways in which sequence variants of peptides and the DNA sequences encoding them may be obtained. For example, recombinant vectors encoding the desired peptide sequence may be treated with mutagenic agents, such as hydroxylamine, to obtain sequence variants. Specific details regarding these methods and protocols are found in the teachings of Maloy *et al.*, 1994; Segal, 1976; Prokop and Bajpai, 1991; Kuby, 1994; and Maniatis *et al.*, 1982, each incorporated herein by reference, for that purpose.

As used herein, the term "oligonucleotide directed mutagenesis procedure" refers to template-dependent processes and vector-mediated propagation which result in an increase in the concentration of a specific nucleic acid molecule relative to its initial concentration, or in an increase in the concentration of a detectable signal, such as amplification. As used herein, the term "oligonucleotide directed mutagenesis procedure" is intended to refer to a process that involves the template-dependent extension of a primer molecule. The term template dependent process refers to nucleic acid synthesis of an RNA or a DNA molecule wherein the sequence of the newly synthesized strand of nucleic acid is dictated by the well-known rules of complementary base pairing (see, for example,

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Watson, 1987). Typically, vector mediated methodologies involve the introduction of the nucleic acid fragment into a DNA or RNA vector, the clonal amplification of the vector, and the recovery of the amplified nucleic acid fragment. Examples of such methodologies are provided by U. S. Patent No. 4,237,224, specifically incorporated herein by reference in its entirety.

## POLYNUCLEOTIDE AMPLIFICATION TECHNIQUES

A number of template dependent processes are available to amplify the target sequences of interest present in a sample. One of the best known amplification methods is the polymerase chain reaction (PCR<sup>TM</sup>) which is described in detail in U.S. Patent Nos. 4,683,195, 4,683,202 and 4,800,159, each of which is incorporated herein by reference in its entirety. Briefly, in PCR<sup>TM</sup>, two primer sequences are prepared which are complementary to regions on opposite complementary strands of the target sequence. An excess of deoxynucleoside triphosphates is added to a reaction mixture along with a DNA polymerase (*e.g.*, *Taq* polymerase). If the target sequence is present in a sample, the primers will bind to the target and the polymerase will cause the primers to be extended along the target sequence by adding on nucleotides. By raising and lowering the temperature of the reaction mixture, the extended primers will dissociate from the target to form reaction products, excess primers will bind to the target and to the reaction product and the process is repeated. Preferably reverse transcription and PCR<sup>TM</sup> amplification procedure may be performed in order to quantify the amount of mRNA amplified. Polymerase chain reaction methodologies are well known in the art.

Another method for amplification is the ligase chain reaction (referred to as LCR), disclosed in Eur. Pat. Appl. Publ. No. 320,308 (specifically incorporated herein by reference in its entirety). In LCR, two complementary probe pairs are prepared, and in the presence of the target sequence, each pair will bind to opposite complementary strands of the target such that they abut. In the presence of a ligase, the two probe pairs will link to form a single unit. By temperature cycling, as in PCR<sup>TM</sup>, bound ligated units dissociate from the target and then serve as "target sequences" for ligation of excess probe pairs. U.S.

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Patent No. 4,883,750, incorporated herein by reference in its entirety, describes an alternative method of amplification similar to LCR for binding probe pairs to a target sequence.

Qbeta Replicase, described in PCT Intl. Pat. Appl. Publ. No. PCT/US87/00880, incorporated herein by reference in its entirety, may also be used as still another amplification method in the present invention. In this method, a replicative sequence of RNA that has a region complementary to that of a target is added to a sample in the presence of an RNA polymerase. The polymerase will copy the replicative sequence that can then be detected.

An isothermal amplification method, in which restriction endonucleases and ligases are used to achieve the amplification of target molecules that contain nucleotide 5'-[α-thio]triphosphates in one strand of a restriction site (Walker *et al.*, 1992, incorporated herein by reference in its entirety), may also be useful in the amplification of nucleic acids in the present invention.

Strand Displacement Amplification (SDA) is another method of carrying out isothermal amplification of nucleic acids which involves multiple rounds of strand displacement and synthesis, *i.e.* nick translation. A similar method, called Repair Chain Reaction (RCR) is another method of amplification which may be useful in the present invention and is involves annealing several probes throughout a region targeted for amplification, followed by a repair reaction in which only two of the four bases are present. The other two bases can be added as biotinylated derivatives for easy detection. A similar approach is used in SDA.

Sequences can also be detected using a cyclic probe reaction (CPR). In CPR, a probe having a 3' and 5' sequences of non-target DNA and an internal or "middle" sequence of the target protein specific RNA is hybridized to DNA which is present in a sample. Upon hybridization, the reaction is treated with RNaseH, and the products of the probe are identified as distinctive products by generating a signal that is released after digestion. The original template is annealed to another cycling probe and the reaction is

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repeated. Thus, CPR involves amplifying a signal generated by hybridization of a probe to a target gene specific expressed nucleic acid.

Still other amplification methods described in Great Britain Pat. Appl. No. 2 202 328, and in PCT Intl. Pat. Appl. Publ. No. PCT/US89/01025, each of which is incorporated herein by reference in its entirety, may be used in accordance with the present invention. In the former application, "modified" primers are used in a PCR-like, template and enzyme dependent synthesis. The primers may be modified by labeling with a capture moiety (e.g., biotin) and/or a detector moiety (e.g., enzyme). In the latter application, an excess of labeled probes is added to a sample. In the presence of the target sequence, the probe binds and is cleaved catalytically. After cleavage, the target sequence is released intact to be bound by excess probe. Cleavage of the labeled probe signals the presence of the target sequence.

Other nucleic acid amplification procedures include transcription-based amplification systems (TAS) (Kwoh et al., 1989; PCT Intl. Pat. Appl. Publ. No. WO 88/10315, incorporated herein by reference in its entirety), including nucleic acid sequence based amplification (NASBA) and 3SR. In NASBA, the nucleic acids can be prepared for amplification by standard phenol/chloroform extraction, heat denaturation of a sample, treatment with lysis buffer and minispin columns for isolation of DNA and RNA or guanidinium chloride extraction of RNA. These amplification techniques involve annealing a primer that has sequences specific to the target sequence. Following polymerization, DNA/RNA hybrids are digested with RNase H while double stranded DNA molecules are heat-denatured again. In either case the single stranded DNA is made fully double stranded by addition of second target-specific primer, followed by polymerization. The double stranded DNA molecules are then multiply transcribed by a polymerase such as T7 or SP6. In an isothermal cyclic reaction, the RNAs are reverse transcribed into DNA, and transcribed once again with a polymerase such as T7 or SP6. The resulting products, whether truncated or complete, indicate target-specific sequences.

Eur. Pat. Appl. Publ. No. 329,822, incorporated herein by reference in its entirety, disclose a nucleic acid amplification process involving cyclically synthesizing

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single-stranded RNA ("ssRNA"), ssDNA, and double-stranded DNA (dsDNA), which may be used in accordance with the present invention. The ssRNA is a first template for a first primer oligonucleotide, which is elongated by reverse transcriptase (RNA-dependent DNA polymerase). The RNA is then removed from resulting DNA:RNA duplex by the action of ribonuclease H (RNase H, an RNase specific for RNA in a duplex with either DNA or RNA). The resultant ssDNA is a second template for a second primer, which also includes the sequences of an RNA polymerase promoter (exemplified by T7 RNA polymerase) 5' to This primer is then extended by DNA polymerase its homology to its template. (exemplified by the large "Klenow" fragment of E. coli DNA polymerase I), resulting as a double-stranded DNA ("dsDNA") molecule, having a sequence identical to that of the original RNA between the primers and having additionally, at one end, a promoter sequence. This promoter sequence can be used by the appropriate RNA polymerase to make many RNA copies of the DNA. These copies can then re-enter the cycle leading to very swift amplification. With proper choice of enzymes, this amplification can be done isothermally without addition of enzymes at each cycle. Because of the cyclical nature of this process, the starting sequence can be chosen to be in the form of either DNA or RNA.

PCT Intl. Pat. Appl. Publ. No. WO 89/06700, incorporated herein by reference in its entirety, disclose a nucleic acid sequence amplification scheme based on the hybridization of a promoter/primer sequence to a target single-stranded DNA ("ssDNA") followed by transcription of many RNA copies of the sequence. This scheme is not cyclic; *i.e.* new templates are not produced from the resultant RNA transcripts. Other amplification methods include "RACE" (Frohman, 1990), and "one-sided PCR" (Ohara, 1989) which are well-known to those of skill in the art.

Methods based on ligation of two (or more) oligonucleotides in the presence of nucleic acid having the sequence of the resulting "di-oligonucleotide", thereby amplifying the di-oligonucleotide (Wu and Dean, 1996, incorporated herein by reference in its entirety), may also be used in the amplification of DNA sequences of the present invention.

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### **BIOLOGICAL FUNCTIONAL EQUIVALENTS**

Modification and changes may be made in the structure of the polynucleotides and polypeptides of the present invention and still obtain a functional molecule that encodes a polypeptide with desirable characteristics. As mentioned above, it is often desirable to introduce one or more mutations into a specific polynucleotide sequence. In certain circumstances, the resulting encoded polypeptide sequence is altered by this mutation, or in other cases, the sequence of the polypeptide is unchanged by one or more mutations in the encoding polynucleotide.

When it is desirable to alter the amino acid sequence of a polypeptide to create an equivalent, or even an improved, second-generation molecule, the amino acid changes may be achieved by changing one or more of the codons of the encoding DNA sequence, according to Table 1.

For example, certain amino acids may be substituted for other amino acids in a protein structure without appreciable loss of interactive binding capacity with structures such as, for example, antigen-binding regions of antibodies or binding sites on substrate molecules. Since it is the interactive capacity and nature of a protein that defines that protein's biological functional activity, certain amino acid sequence substitutions can be made in a protein sequence, and, of course, its underlying DNA coding sequence, and nevertheless obtain a protein with like properties. It is thus contemplated by the inventors that various changes may be made in the peptide sequences of the disclosed compositions, or corresponding DNA sequences which encode said peptides without appreciable loss of their biological utility or activity.

TABLE 1

Amino Acids			Codons					
Alanine	Ala	A	GCA	GCC	GCG	GCU		
Cysteine	Cys	C	UGC	UGU				
Aspartic acid	Asp	D	GAC	GAU				
Glutamic acid	Glu	E	GAA	GAG				
Phenylalanine	Phe	F	UUC	UUU				
Glycine	Gly	G	GGA	GGC	GGG	GGU		
Histidine	His	H	CAC	CAU				
Isoleucine	Ile	I	AUA	AUC	AUU			
Lysine	Lys	K	AAA	AAG				
Leucine	Leu	L	UUA	UUG	CUA	CUC	CUG	CUU
Methionine	Met	M	AUG					
Asparagine	Asn	N	AAC	AAU				
Proline	Pro	P	CCA	CCC	CCG	CCU		
Glutamine	Gln	Q	CAA	CAG				
Arginine	Arg	R	AGA	AGG	CGA	CGC	CGG	CGU
Serine	Ser	S	AGC	AGU	UCA	UCC	UCG	UCU
Threonine	Thr	T	ACA	ACC	ACG	ACU		
Valine	Val	V	GUA	GUC	GUG	GUU		
Tryptophan	Trp	W	UGG					
Tyrosine	Tyr	Y	UAC	UAU				

In making such changes, the hydropathic index of amino acids may be considered. The importance of the hydropathic amino acid index in conferring interactive biologic function on a protein is generally understood in the art (Kyte and Doolittle, 1982, incorporated herein by reference). It is accepted that the relative hydropathic character of the amino acid contributes to the secondary structure of the resultant protein, which in turn defines the interaction of the protein with other molecules, for example, enzymes, substrates, receptors, DNA, antibodies, antigens, and the like. Each amino acid has been

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assigned a hydropathic index on the basis of its hydrophobicity and charge characteristics (Kyte and Doolittle, 1982). These values are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (-0.4); threonine (-0.7); serine (-0.8); tryptophan (-0.9); tyrosine (-1.3); proline (-1.6); histidine (-3.2); glutamate (-3.5); glutamine (-3.5); aspartate (-3.5); asparagine (-3.5); lysine (-3.9); and arginine (-4.5).

It is known in the art that certain amino acids may be substituted by other amino acids having a similar hydropathic index or score and still result in a protein with similar biological activity, *i.e.* still obtain a biological functionally equivalent protein. In making such changes, the substitution of amino acids whose hydropathic indices are within  $\pm 2$  is preferred, those within  $\pm 1$  are particularly preferred, and those within  $\pm 0.5$  are even more particularly preferred. It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity. U. S. Patent 4,554,101 (specifically incorporated herein by reference in its entirety), states that the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with a biological property of the protein.

As detailed in U. S. Patent 4,554,101, the following hydrophilicity values have been assigned to amino acid residues: arginine ( $\pm$ 3.0); lysine ( $\pm$ 3.0); aspartate ( $\pm$ 3.0  $\pm$ 1); glutamate ( $\pm$ 3.0  $\pm$ 1); serine ( $\pm$ 0.3); asparagine ( $\pm$ 0.2); glutamine ( $\pm$ 0.2); glycine (0); threonine ( $\pm$ 0.4); proline ( $\pm$ 0.5  $\pm$ 1); alanine ( $\pm$ 0.5); histidine ( $\pm$ 0.5); cysteine ( $\pm$ 1.0); methionine ( $\pm$ 1.3); valine ( $\pm$ 1.5); leucine ( $\pm$ 1.8); isoleucine ( $\pm$ 1.8); tyrosine ( $\pm$ 2.3); phenylalanine ( $\pm$ 2.5); tryptophan ( $\pm$ 3.4). It is understood that an amino acid can be substituted for another having a similar hydrophilicity value and still obtain a biologically equivalent, and in particular, an immunologically equivalent protein. In such changes, the substitution of amino acids whose hydrophilicity values are within  $\pm$ 2 is preferred, those within  $\pm$ 1 are particularly preferred, and those within  $\pm$ 0.5 are even more particularly preferred.

As outlined above, amino acid substitutions are generally therefore based on the relative similarity of the amino acid side-chain substituents, for example, their

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hydrophobicity, hydrophilicity, charge, size, and the like. Exemplary substitutions that take various of the foregoing characteristics into consideration are well known to those of skill in the art and include: arginine and lysine; glutamate and aspartate; serine and threonine; glutamine and asparagine; and valine, leucine and isoleucine.

In addition, any polynucleotide may be further modified to increase stability *in vivo*. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such as inosine, queosine and wybutosine, as well as acetyl- methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

# IN VIVO POLYNUCLEOTIDE DELIVERY TECHNIQUES

In additional embodiments, genetic constructs comprising one or more of the polynucleotides of the invention are introduced into cells *in vivo*. This may be achieved using any of a variety or well known approaches, several of which are outlined below for the purpose of illustration.

#### 1. ADENOVIRUS

One of the preferred methods for *in vivo* delivery of one or more nucleic acid sequences involves the use of an adenovirus expression vector. "Adenovirus expression vector" is meant to include those constructs containing adenovirus sequences sufficient to (a) support packaging of the construct and (b) to express a polynucleotide that has been cloned therein in a sense or antisense orientation. Of course, in the context of an antisense construct, expression does not require that the gene product be synthesized.

The expression vector comprises a genetically engineered form of an adenovirus. Knowledge of the genetic organization of adenovirus, a 36 kb, linear, double-stranded DNA virus, allows substitution of large pieces of adenoviral DNA with foreign sequences up to 7 kb (Grunhaus and Horwitz, 1992). In contrast to retrovirus, the adenoviral infection of host cells does not result in chromosomal integration because

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adenoviral DNA can replicate in an episomal manner without potential genotoxicity. Also, adenoviruses are structurally stable, and no genome rearrangement has been detected after extensive amplification. Adenovirus can infect virtually all epithelial cells regardless of their cell cycle stage. So far, adenoviral infection appears to be linked only to mild disease such as acute respiratory disease in humans.

Adenovirus is particularly suitable for use as a gene transfer vector because of its mid-sized genome, ease of manipulation, high titer, wide target-cell range and high infectivity. Both ends of the viral genome contain 100-200 base pair inverted repeats (ITRs), which are *cis* elements necessary for viral DNA replication and packaging. The early (E) and late (L) regions of the genome contain different transcription units that are divided by the onset of viral DNA replication. The E1 region (E1A and E1B) encodes proteins responsible for the regulation of transcription of the viral genome and a few cellular genes. The expression of the E2 region (E2A and E2B) results in the synthesis of the proteins for viral DNA replication. These proteins are involved in DNA replication, late gene expression and host cell shut-off (Renan, 1990). The products of the late genes, including the majority of the viral capsid proteins, are expressed only after significant processing of a single primary transcript issued by the major late promoter (MLP). The MLP, (located at 16.8 m.u.) is particularly efficient during the late phase of infection, and all the mRNA's issued from this promoter possess a 5'-tripartite leader (TPL) sequence which makes them preferred mRNA's for translation.

In a current system, recombinant adenovirus is generated from homologous recombination between shuttle vector and provirus vector. Due to the possible recombination between two proviral vectors, wild-type adenovirus may be generated from this process. Therefore, it is critical to isolate a single clone of virus from an individual plaque and examine its genomic structure.

Generation and propagation of the current adenovirus vectors, which are replication deficient, depend on a unique helper cell line, designated 293, which was transformed from human embryonic kidney cells by Ad5 DNA fragments and constitutively expresses E1 proteins (Graham *et al.*, 1977). Since the E3 region is

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dispensable from the adenovirus genome (Jones and Shenk, 1978), the current adenovirus vectors, with the help of 293 cells, carry foreign DNA in either the E1, the D3 or both regions (Graham and Prevec, 1991). In nature, adenovirus can package approximately 105% of the wild-type genome (Ghosh-Choudhury *et al.*, 1987), providing capacity for about 2 extra kB of DNA. Combined with the approximately 5.5 kB of DNA that is replaceable in the E1 and E3 regions, the maximum capacity of the current adenovirus vector is under 7.5 kB, or about 15% of the total length of the vector. More than 80% of the adenovirus viral genome remains in the vector backbone and is the source of vector-borne cytotoxicity. Also, the replication deficiency of the E1-deleted virus is incomplete. For example, leakage of viral gene expression has been observed with the currently available vectors at high multiplicities of infection (MOI) (Mulligan, 1993).

Helper cell lines may be derived from human cells such as human embryonic kidney cells, muscle cells, hematopoietic cells or other human embryonic mesenchymal or epithelial cells. Alternatively, the helper cells may be derived from the cells of other mammalian species that are permissive for human adenovirus. Such cells include, *e.g.*, Vero cells or other monkey embryonic mesenchymal or epithelial cells. As stated above, the currently preferred helper cell line is 293.

Recently, Racher *et al.* (1995) disclosed improved methods for culturing 293 cells and propagating adenovirus. In one format, natural cell aggregates are grown by inoculating individual cells into 1 liter siliconized spinner flasks (Techne, Cambridge, UK) containing 100-200 ml of medium. Following stirring at 40 rpm, the cell viability is estimated with trypan blue. In another format, Fibra-Cel microcarriers (Bibby Sterlin, Stone, UK) (5 g/l) is employed as follows. A cell inoculum, resuspended in 5 ml of medium, is added to the carrier (50 ml) in a 250 ml Erlenmeyer flask and left stationary, with occasional agitation, for 1 to 4 h. The medium is then replaced with 50 ml of fresh medium and shaking initiated. For virus production, cells are allowed to grow to about 80% confluence, after which time the medium is replaced (to 25% of the final volume) and adenovirus added at an MOI of 0.05. Cultures are left stationary overnight, following which the volume is increased to 100% and shaking commenced for another 72 h.

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Other than the requirement that the adenovirus vector be replication defective, or at least conditionally defective, the nature of the adenovirus vector is not believed to be crucial to the successful practice of the invention. The adenovirus may be of any of the 42 different known serotypes or subgroups A-F. Adenovirus type 5 of subgroup C is the preferred starting material in order to obtain a conditional replication-defective adenovirus vector for use in the present invention, since Adenovirus type 5 is a human adenovirus about which a great deal of biochemical and genetic information is known, and it has historically been used for most constructions employing adenovirus as a vector.

As stated above, the typical vector according to the present invention is replication defective and will not have an adenovirus E1 region. Thus, it will be most convenient to introduce the polynucleotide encoding the gene of interest at the position from which the E1-coding sequences have been removed. However, the position of insertion of the construct within the adenovirus sequences is not critical to the invention. The polynucleotide encoding the gene of interest may also be inserted in lieu of the deleted E3 region in E3 replacement vectors as described by Karlsson *et al.* (1986) or in the E4 region where a helper cell line or helper virus complements the E4 defect.

Adenovirus is easy to grow and manipulate and exhibits broad host range *in vitro* and *in vivo*. This group of viruses can be obtained in high titers, *e.g.*,  $10^9$ - $10^{11}$  plaque-forming units per ml, and they are highly infective. The life cycle of adenovirus does not require integration into the host cell genome. The foreign genes delivered by adenovirus vectors are episomal and, therefore, have low genotoxicity to host cells. No side effects have been reported in studies of vaccination with wild-type adenovirus (Couch *et al.*, 1963; Top *et al.*, 1971), demonstrating their safety and therapeutic potential as *in vivo* gene transfer vectors.

Adenovirus vectors have been used in eukaryotic gene expression (Levrero et al., 1991; Gomez-Foix et al., 1992) and vaccine development (Grunhaus and Horwitz, 1992; Graham and Prevec, 1992). Recently, animal studies suggested that recombinant adenovirus could be used for gene therapy (Stratford-Perricaudet and Perricaudet, 1991; Stratford-Perricaudet et al., 1990; Rich et al., 1993). Studies in administering recombinant

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adenovirus to different tissues include trachea instillation (Rosenfeld *et al.*, 1991; Rosenfeld *et al.*, 1992), muscle injection (Ragot *et al.*, 1993), peripheral intravenous injections (Herz and Gerard, 1993) and stereotactic inoculation into the brain (Le Gal La Salle *et al.*, 1993).

### 5 2. Retroviruses

The retroviruses are a group of single-stranded RNA viruses characterized by an ability to convert their RNA to double-stranded DNA in infected cells by a process of reverse-transcription (Coffin, 1990). The resulting DNA then stably integrates into cellular chromosomes as a provirus and directs synthesis of viral proteins. The integration results in the retention of the viral gene sequences in the recipient cell and its descendants. The retroviral genome contains three genes, gag, pol, and env that code for capsid proteins, polymerase enzyme, and envelope components, respectively. A sequence found upstream from the gag gene contains a signal for packaging of the genome into virions. Two long terminal repeat (LTR) sequences are present at the 5' and 3' ends of the viral genome. These contain strong promoter and enhancer sequences and are also required for integration in the host cell genome (Coffin, 1990).

In order to construct a retroviral vector, a nucleic acid encoding one or more oligonucleotide or polynucleotide sequences of interest is inserted into the viral genome in the place of certain viral sequences to produce a virus that is replication-defective. In order to produce virions, a packaging cell line containing the gag, pol, and env genes but without the LTR and packaging components is constructed (Mann *et al.*, 1983). When a recombinant plasmid containing a cDNA, together with the retroviral LTR and packaging sequences is introduced into this cell line (by calcium phosphate precipitation for example), the packaging sequence allows the RNA transcript of the recombinant plasmid to be packaged into viral particles, which are then secreted into the culture media (Nicolas and Rubenstein, 1988; Temin, 1986; Mann *et al.*, 1983). The media containing the recombinant retroviruses is then collected, optionally concentrated, and used for gene

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transfer. Retroviral vectors are able to infect a broad variety of cell types. However, integration and stable expression require the division of host cells (Paskind *et al.*, 1975).

A novel approach designed to allow specific targeting of retrovirus vectors was recently developed based on the chemical modification of a retrovirus by the chemical addition of lactose residues to the viral envelope. This modification could permit the specific infection of hepatocytes *via* sialoglycoprotein receptors.

A different approach to targeting of recombinant retroviruses was designed in which biotinylated antibodies against a retroviral envelope protein and against a specific cell receptor were used. The antibodies were coupled *via* the biotin components by using streptavidin (Roux *et al.*, 1989). Using antibodies against major histocompatibility complex class I and class II antigens, they demonstrated the infection of a variety of human cells that bore those surface antigens with an ecotropic virus *in vitro* (Roux *et al.*, 1989).

## 3. ADENO-ASSOCIATED VIRUSES

AAV (Ridgeway, 1988; Hermonat and Muzycska, 1984) is a parovirus, discovered as a contamination of adenoviral stocks. It is a ubiquitous virus (antibodies are present in 85% of the US human population) that has not been linked to any disease. It is also classified as a dependovirus, because its replications is dependent on the presence of a helper virus, such as adenovirus. Five serotypes have been isolated, of which AAV-2 is the best characterized. AAV has a single-stranded linear DNA that is encapsidated into capsid proteins VP1, VP2 and VP3 to form an icosahedral virion of 20 to 24 nm in diameter (Muzyczka and McLaughlin, 1988).

The AAV DNA is approximately 4.7 kilobases long. It contains two open reading frames and is flanked by two ITRs. There are two major genes in the AAV genome: *rep* and *cap*. The *rep* gene codes for proteins responsible for viral replications, whereas *cap* codes for capsid protein VP1-3. Each ITR forms a T-shaped hairpin structure. These terminal repeats are the only essential *cis* components of the AAV for chromosomal integration. Therefore, the AAV can be used as a vector with all viral coding sequences removed and replaced by the cassette of genes for delivery. Three viral

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promoters have been identified and named p5, p19, and p40, according to their map position. Transcription from p5 and p19 results in production of rep proteins, and transcription from p40 produces the capsid proteins (Hermonat and Muzyczka, 1984).

There are several factors that prompted researchers to study the possibility of using rAAV as an expression vector. One is that the requirements for delivering a gene to integrate into the host chromosome are surprisingly few. It is necessary to have the 145-bp ITRs, which are only 6% of the AAV genome. This leaves room in the vector to assemble a 4.5-kb DNA insertion. While this carrying capacity may prevent the AAV from delivering large genes, it is amply suited for delivering the antisense constructs of the present invention.

AAV is also a good choice of delivery vehicles due to its safety. There is a relatively complicated rescue mechanism: not only wild type adenovirus but also AAV genes are required to mobilize rAAV. Likewise, AAV is not pathogenic and not associated with any disease. The removal of viral coding sequences minimizes immune reactions to viral gene expression, and therefore, rAAV does not evoke an inflammatory response.

## 4. OTHER VIRAL VECTORS AS EXPRESSION CONSTRUCTS

Other viral vectors may be employed as expression constructs in the present invention for the delivery of oligonucleotide or polynucleotide sequences to a host cell. Vectors derived from viruses such as vaccinia virus (Ridgeway, 1988; Coupar *et al.*, 1988), lentiviruses, polio viruses and herpes viruses may be employed. They offer several attractive features for various mammalian cells (Friedmann, 1989; Ridgeway, 1988; Coupar *et al.*, 1988; Horwich *et al.*, 1990).

With the recent recognition of defective hepatitis B viruses, new insight was gained into the structure-function relationship of different viral sequences. *In vitro* studies showed that the virus could retain the ability for helper-dependent packaging and reverse transcription despite the deletion of up to 80% of its genome (Horwich *et al.*, 1990). This suggested that large portions of the genome could be replaced with foreign genetic material. The hepatotropism and persistence (integration) were particularly attractive

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properties for liver-directed gene transfer. Chang *et al.* (1991) introduced the chloramphenical acetyltransferase (CAT) gene into duck hepatitis B virus genome in the place of the polymerase, surface, and pre-surface coding sequences. It was cotransfected with wild-type virus into an avian hepatoma cell line. Culture media containing high titers of the recombinant virus were used to infect primary duckling hepatocytes. Stable CAT gene expression was detected for at least 24 days after transfection (Chang *et al.*, 1991).

## 5. Non-viral vectors

In order to effect expression of the oligonucleotide or polynucleotide sequences of the present invention, the expression construct must be delivered into a cell. This delivery may be accomplished *in vitro*, as in laboratory procedures for transforming cells lines, or *in vivo* or *ex vivo*, as in the treatment of certain disease states. As described above, one preferred mechanism for delivery is *via* viral infection where the expression construct is encapsulated in an infectious viral particle.

Once the expression construct has been delivered into the cell the nucleic acid encoding the desired oligonucleotide or polynucleotide sequences may be positioned and expressed at different sites. In certain embodiments, the nucleic acid encoding the construct may be stably integrated into the genome of the cell. This integration may be in the specific location and orientation *via* homologous recombination (gene replacement) or it may be integrated in a random, non-specific location (gene augmentation). In yet further embodiments, the nucleic acid may be stably maintained in the cell as a separate, episomal segment of DNA. Such nucleic acid segments or "episomes" encode sequences sufficient to permit maintenance and replication independent of or in synchronization with the host cell cycle. How the expression construct is delivered to a cell and where in the cell the nucleic acid remains is dependent on the type of expression construct employed.

In certain embodiments of the invention, the expression construct comprising one or more oligonucleotide or polynucleotide sequences may simply consist of naked recombinant DNA or plasmids. Transfer of the construct may be performed by any of the methods mentioned above which physically or chemically permeabilize the cell

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membrane. This is particularly applicable for transfer *in vitro* but it may be applied to *in vivo* use as well. Dubensky *et al.* (1984) successfully injected polyomavirus DNA in the form of calcium phosphate precipitates into liver and spleen of adult and newborn mice demonstrating active viral replication and acute infection. Benvenisty and Reshef (1986) also demonstrated that direct intraperitoneal injection of calcium phosphate-precipitated plasmids results in expression of the transfected genes. It is envisioned that DNA encoding a gene of interest may also be transferred in a similar manner *in vivo* and express the gene product.

Another embodiment of the invention for transferring a naked DNA expression construct into cells may involve particle bombardment. This method depends on the ability to accelerate DNA-coated microprojectiles to a high velocity allowing them to pierce cell membranes and enter cells without killing them (Klein *et al.*, 1987). Several devices for accelerating small particles have been developed. One such device relies on a high voltage discharge to generate an electrical current, which in turn provides the motive force (Yang *et al.*, 1990). The microprojectiles used have consisted of biologically inert substances such as tungsten or gold beads.

Selected organs including the liver, skin, and muscle tissue of rats and mice have been bombarded *in vivo* (Yang *et al.*, 1990; Zelenin *et al.*, 1991). This may require surgical exposure of the tissue or cells, to eliminate any intervening tissue between the gun and the target organ, *i.e. ex vivo* treatment. Again, DNA encoding a particular gene may be delivered *via* this method and still be incorporated by the present invention.

#### ANTISENSE OLIGONUCLEOTIDES

The end result of the flow of genetic information is the synthesis of protein. DNA is transcribed by polymerases into messenger RNA and translated on the ribosome to yield a folded, functional protein. Thus there are several steps along the route where protein synthesis can be inhibited. The native DNA segment coding for a polypeptide described herein, as all such mammalian DNA strands, has two strands: a sense strand and an antisense strand held together by hydrogen bonding. The messenger RNA coding for

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polypeptide has the same nucleotide sequence as the sense DNA strand except that the DNA thymidine is replaced by uridine. Thus, synthetic antisense nucleotide sequences will bind to a mRNA and inhibit expression of the protein encoded by that mRNA.

The targeting of antisense oligonucleotides to mRNA is thus one mechanism to shut down protein synthesis, and, consequently, represents a powerful and targeted therapeutic approach. For example, the synthesis of polygalactauronase and the muscarine type 2 acetylcholine receptor are inhibited by antisense oligonucleotides directed to their respective mRNA sequences (U. S. Patent 5,739,119 and U. S. Patent 5,759,829, each specifically incorporated herein by reference in its entirety). Further, examples of antisense inhibition have been demonstrated with the nuclear protein cyclin, the multiple drug resistance gene (MDG1), ICAM-1, E-selectin, STK-1, striatal GABA<sub>A</sub> receptor and human EGF (Jaskulski *et al.*, 1988; Vasanthakumar and Ahmed, 1989; Peris *et al.*, 1998; U. S. Patent 5,801,154; U. S. Patent 5,789,573; U. S. Patent 5,718,709 and U. S. Patent 5,610,288, each specifically incorporated herein by reference in its entirety). Antisense constructs have also been described that inhibit and can be used to treat a variety of abnormal cellular proliferations, *e.g.* cancer (U. S. Patent 5,747,470; U. S. Patent 5,591,317 and U. S. Patent 5,783,683, each specifically incorporated herein by reference in its entirety).

Therefore. exemplary embodiments, in the invention provides oligonucleotide sequences that comprise all, or a portion of, any sequence that is capable of specifically binding to polynucleotide sequence described herein, or a complement thereof. In one embodiment, the antisense oligonucleotides comprise DNA or derivatives thereof. In another embodiment, the oligonucleotides comprise RNA or derivatives thereof. In a third embodiment, the oligonucleotides are modified DNAs comprising phosphorothioated modified backbone. In a fourth embodiment, the oligonucleotide sequences comprise peptide nucleic acids or derivatives thereof. In each case, preferred compositions comprise a sequence region that is complementary, and more preferably substantially-complementary, and even more preferably, completely complementary to one or more portions of polynucleotides disclosed herein.

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Selection of antisense compositions specific for a given gene sequence is based upon analysis of the chosen target sequence (*i.e.* in these illustrative examples the rat and human sequences) and determination of secondary structure, T<sub>m</sub>, binding energy, relative stability, and antisense compositions were selected based upon their relative inability to form dimers, hairpins, or other secondary structures that would reduce or prohibit specific binding to the target mRNA in a host cell.

Highly preferred target regions of the mRNA, are those which are at or near the AUG translation initiation codon, and those sequences which were substantially complementary to 5' regions of the mRNA. These secondary structure analyses and target site selection considerations were performed using v.4 of the OLIGO primer analysis software (Rychlik, 1997) and the BLASTN 2.0.5 algorithm software (Altschul *et al.*, 1997).

The use of an antisense delivery method employing a short peptide vector, termed MPG (27 residues), is also contemplated. The MPG peptide contains a hydrophobic domain derived from the fusion sequence of HIV gp41 and a hydrophilic domain from the nuclear localization sequence of SV40 T-antigen (Morris *et al.*, 1997). It has been demonstrated that several molecules of the MPG peptide coat the antisense oligonucleotides and can be delivered into cultured mammalian cells in less than 1 hour with relatively high efficiency (90%). Further, the interaction with MPG strongly increases both the stability of the oligonucleotide to nuclease and the ability to cross the plasma membrane (Morris *et al.*, 1997).

### **RIBOZYMES**

Although proteins traditionally have been used for catalysis of nucleic acids, another class of macromolecules has emerged as useful in this endeavor. Ribozymes are RNA-protein complexes that cleave nucleic acids in a site-specific fashion. Ribozymes have specific catalytic domains that possess endonuclease activity (Kim and Cech, 1987; Gerlach *et al.*, 1987; Forster and Symons, 1987). For example, a large number of ribozymes accelerate phosphoester transfer reactions with a high degree of specificity, often cleaving only one of several phosphoesters in an oligonucleotide substrate (Cech *et* 

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al., 1981; Michel and Westhof, 1990; Reinhold-Hurek and Shub, 1992). This specificity has been attributed to the requirement that the substrate bind via specific base-pairing interactions to the internal guide sequence ("IGS") of the ribozyme prior to chemical reaction.

Ribozyme catalysis has primarily been observed as part of sequence-specific cleavage/ligation reactions involving nucleic acids (Joyce, 1989; Cech et al., 1981). For example, U. S. Patent No. 5,354,855 (specifically incorporated herein by reference) reports that certain ribozymes can act as endonucleases with a sequence specificity greater than that of known ribonucleases and approaching that of the DNA restriction enzymes. Thus, sequence-specific ribozyme-mediated inhibition of gene expression may be particularly suited to therapeutic applications (Scanlon et al., 1991; Sarver et al., 1990). Recently, it was reported that ribozymes elicited genetic changes in some cells lines to which they were applied; the altered genes included the oncogenes H-ras, c-fos and genes of HIV. Most of this work involved the modification of a target mRNA, based on a specific mutant codon that is cleaved by a specific ribozyme.

Six basic varieties of naturally-occurring enzymatic RNAs are known presently. Each can catalyze the hydrolysis of RNA phosphodiester bonds *in trans* (and thus can cleave other RNA molecules) under physiological conditions. In general, enzymatic nucleic acids act by first binding to a target RNA. Such binding occurs through the target binding portion of a enzymatic nucleic acid which is held in close proximity to an enzymatic portion of the molecule that acts to cleave the target RNA. Thus, the enzymatic nucleic acid first recognizes and then binds a target RNA through complementary base-pairing, and once bound to the correct site, acts enzymatically to cut the target RNA. Strategic cleavage of such a target RNA will destroy its ability to direct synthesis of an encoded protein. After an enzymatic nucleic acid has bound and cleaved its RNA target, it is released from that RNA to search for another target and can repeatedly bind and cleave new targets.

The enzymatic nature of a ribozyme is advantageous over many technologies, such as antisense technology (where a nucleic acid molecule simply binds to

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a nucleic acid target to block its translation) since the concentration of ribozyme necessary to affect a therapeutic treatment is lower than that of an antisense oligonucleotide. This advantage reflects the ability of the ribozyme to act enzymatically. Thus, a single ribozyme molecule is able to cleave many molecules of target RNA. In addition, the ribozyme is a highly specific inhibitor, with the specificity of inhibition depending not only on the base pairing mechanism of binding to the target RNA, but also on the mechanism of target RNA cleavage. Single mismatches, or base-substitutions, near the site of cleavage can completely eliminate catalytic activity of a ribozyme. Similar mismatches in antisense molecules do not prevent their action (Woolf *et al.*, 1992). Thus, the specificity of action of a ribozyme is greater than that of an antisense oligonucleotide binding the same RNA site.

The enzymatic nucleic acid molecule may be formed in a hammerhead, hairpin, a hepatitis δ virus, group I intron or RNaseP RNA (in association with an RNA guide sequence) or Neurospora VS RNA motif. Examples of hammerhead motifs are described by Rossi et al. (1992). Examples of hairpin motifs are described by Hampel et al. (Eur. Pat. Appl. Publ. No. EP 0360257), Hampel and Tritz (1989), Hampel et al. (1990) and U. S. Patent 5,631,359 (specifically incorporated herein by reference). An example of the hepatitis  $\delta$  virus motif is described by Perrotta and Been (1992); an example of the RNaseP motif is described by Guerrier-Takada et al. (1983); Neurospora VS RNA ribozyme motif is described by Collins (Saville and Collins, 1990; Saville and Collins, 1991; Collins and Olive, 1993); and an example of the Group I intron is described in (U.S. Patent 4,987,071, specifically incorporated herein by reference). All that is important in an enzymatic nucleic acid molecule of this invention is that it has a specific substrate binding site which is complementary to one or more of the target gene RNA regions, and that it have nucleotide sequences within or surrounding that substrate binding site which impart an RNA cleaving activity to the molecule. Thus the ribozyme constructs need not be limited to specific motifs mentioned herein.

In certain embodiments, it may be important to produce enzymatic cleaving agents which exhibit a high degree of specificity for the RNA of a desired target, such as

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one of the sequences disclosed herein. The enzymatic nucleic acid molecule is preferably targeted to a highly conserved sequence region of a target mRNA. Such enzymatic nucleic acid molecules can be delivered exogenously to specific cells as required. Alternatively, the ribozymes can be expressed from DNA or RNA vectors that are delivered to specific cells.

Small enzymatic nucleic acid motifs (e.g., of the hammerhead or the hairpin structure) may also be used for exogenous delivery. The simple structure of these molecules increases the ability of the enzymatic nucleic acid to invade targeted regions of the mRNA structure. Alternatively, catalytic RNA molecules can be expressed within cells from eukaryotic promoters (e.g., Scanlon et al., 1991; Kashani-Sabet et al., 1992; Dropulic et al., 1992; Weerasinghe et al., 1991; Ojwang et al., 1992; Chen et al., 1992; Sarver et al., 1990). Those skilled in the art realize that any ribozyme can be expressed in eukaryotic cells from the appropriate DNA vector. The activity of such ribozymes can be augmented by their release from the primary transcript by a second ribozyme (Int. Pat. Appl. Publ. No. WO 93/23569, and Int. Pat. Appl. Publ. No. WO 94/02595, both hereby incorporated by reference; Ohkawa et al., 1992; Taira et al., 1991; and Ventura et al., 1993).

Ribozymes may be added directly, or can be complexed with cationic lipids, lipid complexes, packaged within liposomes, or otherwise delivered to target cells. The RNA or RNA complexes can be locally administered to relevant tissues *ex vivo*, or *in vivo* through injection, aerosol inhalation, infusion pump or stent, with or without their incorporation in biopolymers.

Ribozymes may be designed as described in Int. Pat. Appl. Publ. No. WO 93/23569 and Int. Pat. Appl. Publ. No. WO 94/02595, each specifically incorporated herein by reference) and synthesized to be tested *in vitro* and *in vivo*, as described. Such ribozymes can also be optimized for delivery. While specific examples are provided, those in the art will recognize that equivalent RNA targets in other species can be utilized when necessary.

Hammerhead or hairpin ribozymes may be individually analyzed by computer folding (Jaeger et al., 1989) to assess whether the ribozyme sequences fold into

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the appropriate secondary structure. Those ribozymes with unfavorable intramolecular interactions between the binding arms and the catalytic core are eliminated from consideration. Varying binding arm lengths can be chosen to optimize activity. Generally, at least 5 or so bases on each arm are able to bind to, or otherwise interact with, the target RNA.

Ribozymes of the hammerhead or hairpin motif may be designed to anneal to various sites in the mRNA message, and can be chemically synthesized. The method of synthesis used follows the procedure for normal RNA synthesis as described in Usman et al. (1987) and in Scaringe et al. (1990) and makes use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5'-end, and phosphoramidites at the 3'-end. Average stepwise coupling yields are typically >98%. Hairpin ribozymes may be synthesized in two parts and annealed to reconstruct an active ribozyme (Chowrira and Burke, 1992). Ribozymes may be modified extensively to enhance stability by modification with nuclease resistant groups, for example, 2'-amino, 2'-C-allyl, 2'-flouro, 2'-o-methyl, 2'-H (for a review see e.g., Usman and Cedergren, 1992). Ribozymes may be purified by gel electrophoresis using general methods or by high pressure liquid chromatography and resuspended in water.

Ribozyme activity can be optimized by altering the length of the ribozyme binding arms, or chemically synthesizing ribozymes with modifications that prevent their degradation by serum ribonucleases (see *e.g.*, Int. Pat. Appl. Publ. No. WO 92/07065; Perrault *et al*, 1990; Pieken *et al.*, 1991; Usman and Cedergren, 1992; Int. Pat. Appl. Publ. No. WO 93/15187; Int. Pat. Appl. Publ. No. WO 91/03162; Eur. Pat. Appl. Publ. No. 92110298.4; U. S. Patent 5,334,711; and Int. Pat. Appl. Publ. No. WO 94/13688, which describe various chemical modifications that can be made to the sugar moieties of enzymatic RNA molecules), modifications which enhance their efficacy in cells, and removal of stem II bases to shorten RNA synthesis times and reduce chemical requirements.

Sullivan et al. (Int. Pat. Appl. Publ. No. WO 94/02595) describes the general methods for delivery of enzymatic RNA molecules. Ribozymes may be

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administered to cells by a variety of methods known to those familiar to the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as hydrogels, cyclodextrins, biodegradable nanocapsules, and bioadhesive microspheres. For some indications, ribozymes may be directly delivered *ex vivo* to cells or tissues with or without the aforementioned vehicles. Alternatively, the RNA/vehicle combination may be locally delivered by direct inhalation, by direct injection or by use of a catheter, infusion pump or stent. Other routes of delivery include, but are not limited to, intravascular, intramuscular, subcutaneous or joint injection, aerosol inhalation, oral (tablet or pill form), topical, systemic, ocular, intraperitoneal and/or intrathecal delivery. More detailed descriptions of ribozyme delivery and administration are provided in Int. Pat. Appl. Publ. No. WO 94/02595 and Int. Pat. Appl. Publ. No. WO 93/23569, each specifically incorporated herein by reference.

Another means of accumulating high concentrations of a ribozyme(s) within cells is to incorporate the ribozyme-encoding sequences into a DNA expression vector. Transcription of the ribozyme sequences are driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA polymerase III (pol III). Transcripts from pol II or pol III promoters will be expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type will depend on the nature of the gene regulatory sequences (enhancers, silencers, etc.) present nearby. Prokaryotic RNA polymerase promoters may also be used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells (Elroy-Stein and Moss, 1990; Gao and Huang, 1993; Lieber et al., 1993; Zhou et al., 1990). Ribozymes expressed from such promoters can function in mammalian cells (e.g. Kashani-Saber et al., 1992; Ojwang et al., 1992; Chen et al., 1992; Yu et al., 1993; L'Huillier et al., 1992; Lisziewicz et al., 1993). Such transcription units can be incorporated into a variety of vectors for introduction into mammalian cells, including but not restricted to, plasmid DNA vectors, viral DNA vectors (such as adenovirus or adeno-associated vectors), or viral RNA vectors (such as retroviral, semliki forest virus, sindbis virus vectors).

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Ribozymes may be used as diagnostic tools to examine genetic drift and mutations within diseased cells. They can also be used to assess levels of the target RNA molecule. The close relationship between ribozyme activity and the structure of the target RNA allows the detection of mutations in any region of the molecule which alters the basepairing and three-dimensional structure of the target RNA. By using multiple ribozymes, one may map nucleotide changes which are important to RNA structure and function in vitro, as well as in cells and tissues. Cleavage of target RNAs with ribozymes may be used to inhibit gene expression and define the role (essentially) of specified gene products in the progression of disease. In this manner, other genetic targets may be defined as important mediators of the disease. These studies will lead to better treatment of the disease progression by affording the possibility of combinational therapies (e.g., multiple ribozymes targeted to different genes, ribozymes coupled with known small molecule inhibitors, or intermittent treatment with combinations of ribozymes and/or other chemical or biological molecules). Other in vitro uses of ribozymes are well known in the art, and include detection of the presence of mRNA associated with an IL-5 related condition. Such RNA is detected by determining the presence of a cleavage product after treatment with a ribozyme using standard methodology.

#### PEPTIDE NUCLEIC ACIDS

In certain embodiments, the inventors contemplate the use of peptide nucleic acids (PNAs) in the practice of the methods of the invention. PNA is a DNA mimic in which the nucleobases are attached to a pseudopeptide backbone (Good and Nielsen, 1997). PNA is able to be utilized in a number methods that traditionally have used RNA or DNA. Often PNA sequences perform better in techniques than the corresponding RNA or DNA sequences and have utilities that are not inherent to RNA or DNA. A review of PNA including methods of making, characteristics of, and methods of using, is provided by Corey (1997) and is incorporated herein by reference. As such, in certain embodiments, one may prepare PNA sequences that are complementary to one or more portions of the ACE mRNA sequence, and such PNA compositions may be used to regulate, alter,

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decrease, or reduce the translation of ACE-specific mRNA, and thereby alter the level of ACE activity in a host cell to which such PNA compositions have been administered.

PNAs have 2-aminoethyl-glycine linkages replacing the normal phosphodiester backbone of DNA (Nielsen *et al.*, 1991; Hanvey *et al.*, 1992; Hyrup and Nielsen, 1996; Neilsen, 1996). This chemistry has three important consequences: firstly, in contrast to DNA or phosphorothioate oligonucleotides, PNAs are neutral molecules; secondly, PNAs are achiral, which avoids the need to develop a stereoselective synthesis; and thirdly, PNA synthesis uses standard Boc (Dueholm *et al.*, 1994) or Fmoc (Thomson *et al.*, 1995) protocols for solid-phase peptide synthesis, although other methods, including a modified Merrifield method, have been used (Christensen *et al.*, 1995).

PNA monomers or ready-made oligomers are commercially available from PerSeptive Biosystems (Framingham, MA). PNA syntheses by either Boc or Fmoc protocols are straightforward using manual or automated protocols (Norton *et al.*, 1995). The manual protocol lends itself to the production of chemically modified PNAs or the simultaneous synthesis of families of closely related PNAs.

As with peptide synthesis, the success of a particular PNA synthesis will depend on the properties of the chosen sequence. For example, while in theory PNAs can incorporate any combination of nucleotide bases, the presence of adjacent purines can lead to deletions of one or more residues in the product. In expectation of this difficulty, it is suggested that, in producing PNAs with adjacent purines, one should repeat the coupling of residues likely to be added inefficiently. This should be followed by the purification of PNAs by reverse-phase high-pressure liquid chromatography (Norton *et al.*, 1995) providing yields and purity of product similar to those observed during the synthesis of peptides.

Modifications of PNAs for a given application may be accomplished by coupling amino acids during solid-phase synthesis or by attaching compounds that contain a carboxylic acid group to the exposed N-terminal amine. Alternatively, PNAs can be modified after synthesis by coupling to an introduced lysine or cysteine. The ease with which PNAs can be modified facilitates optimization for better solubility or for specific

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functional requirements. Once synthesized, the identity of PNAs and their derivatives can be confirmed by mass spectrometry. Several studies have made and utilized modifications of PNAs (Norton *et al.*, 1995; Haaima *et al.*, 1996; Stetsenko *et al.*, 1996; Petersen *et al.*, 1995; Ulmann *et al.*, 1996; Koch *et al.*, 1995; Orum *et al.*, 1995; Footer *et al.*, 1996; Griffith *et al.*, 1995; Kremsky *et al.*, 1996; Pardridge *et al.*, 1995; Boffa *et al.*, 1995; Landsdorp *et al.*, 1996; Gambacorti-Passerini *et al.*, 1996; Armitage *et al.*, 1997; Seeger *et al.*, 1997; Ruskowski *et al.*, 1997). U.S. Patent No. 5,700,922 discusses PNA-DNA-PNA chimeric molecules and their uses in diagnostics, modulating protein in organisms, and treatment of conditions susceptible to therapeutics.

In contrast to DNA and RNA, which contain negatively charged linkages, the PNA backbone is neutral. In spite of this dramatic alteration, PNAs recognize complementary DNA and RNA by Watson-Crick pairing (Egholm *et al.*, 1993), validating the initial modeling by Nielsen *et al.* (1991). PNAs lack 3' to 5' polarity and can bind in either parallel or antiparallel fashion, with the antiparallel mode being preferred (Egholm *et al.*, 1993).

Hybridization of DNA oligonucleotides to DNA and RNA is destabilized by electrostatic repulsion between the negatively charged phosphate backbones of the complementary strands. By contrast, the absence of charge repulsion in PNA-DNA or PNA-RNA duplexes increases the melting temperature ( $T_{\rm m}$ ) and reduces the dependence of  $T_{\rm m}$  on the concentration of mono- or divalent cations (Nielsen *et al.*, 1991). The enhanced rate and affinity of hybridization are significant because they are responsible for the surprising ability of PNAs to perform strand invasion of complementary sequences within relaxed double-stranded DNA. In addition, the efficient hybridization at inverted repeats suggests that PNAs can recognize secondary structure effectively within double-stranded DNA. Enhanced recognition also occurs with PNAs immobilized on surfaces, and Wang *et al.*, 1996).

One might expect that tight binding of PNAs to complementary sequences would also increase binding to similar (but not identical) sequences, reducing the sequence

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specificity of PNA recognition. As with DNA hybridization, however, selective recognition can be achieved by balancing oligomer length and incubation temperature. Moreover, selective hybridization of PNAs is encouraged by PNA-DNA hybridization being less tolerant of base mismatches than DNA-DNA hybridization. For example, a single mismatch within a 16 bp PNA-DNA duplex can reduce the  $T_{\rm m}$  by up to 15°C (Egholm *et al.*, 1993). This high level of discrimination has allowed the development of several PNA-based strategies for the analysis of point mutations (Wang *et al.*, 1996; Carlsson *et al.*, 1996; Thiede *et al.*, 1996; Webb and Hurskainen, 1996; Perry-O'Keefe *et al.*, 1996).

High-affinity binding provides clear advantages for molecular recognition and the development of new applications for PNAs. For example, 11-13 nucleotide PNAs inhibit the activity of telomerase, a ribonucleo-protein that extends telomere ends using an essential RNA template, while the analogous DNA oligomers do not (Norton *et al.*, 1996).

Neutral PNAs are more hydrophobic than analogous DNA oligomers, and this can lead to difficulty solubilizing them at neutral pH, especially if the PNAs have a high purine content or if they have the potential to form secondary structures. Their solubility can be enhanced by attaching one or more positive charges to the PNA termini (Nielsen *et al.*, 1991).

Findings by Allfrey and colleagues suggest that strand invasion will occur spontaneously at sequences within chromosomal DNA (Boffa *et al.*, 1995; Boffa *et al.*, 1996). These studies targeted PNAs to triplet repeats of the nucleotides CAG and used this recognition to purify transcriptionally active DNA (Boffa *et al.*, 1995) and to inhibit transcription (Boffa *et al.*, 1996). This result suggests that if PNAs can be delivered within cells then they will have the potential to be general sequence-specific regulators of gene expression. Studies and reviews concerning the use of PNAs as antisense and anti-gene agents include Nielsen *et al.* (1993b), Hanvey *et al.* (1992), and Good and Nielsen (1997). Koppelhus *et al.* (1997) have used PNAs to inhibit HIV-1 inverse transcription, showing that PNAs may be used for antiviral therapies.

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Methods of characterizing the antisense binding properties of PNAs are discussed in Rose (1993) and Jensen *et al.* (1997). Rose uses capillary gel electrophoresis to determine binding of PNAs to their complementary oligonucleotide, measuring the relative binding kinetics and stoichiometry. Similar types of measurements were made by Jensen *et al.* using BIAcore<sup>TM</sup> technology.

Other applications of PNAs include use in DNA strand invasion (Nielsen et al., 1991), antisense inhibition (Hanvey et al., 1992), mutational analysis (Orum et al., 1993), enhancers of transcription (Mollegaard et al., 1994), nucleic acid purification (Orum et al., 1995), isolation of transcriptionally active genes (Boffa et al., 1995), blocking of transcription factor binding (Vickers et al., 1995), genome cleavage (Veselkov et al., 1996), biosensors (Wang et al., 1996), in situ hybridization (Thisted et al., 1996), and in a alternative to Southern blotting (Perry-O'Keefe, 1996).

# POLYPEPTIDE COMPOSITIONS

The present invention, in other aspects, provides polypeptide compositions. Generally, a polypeptide of the invention will be an isolated polypeptide (or an epitope, variant, or active fragment thereof) derived from a mammalian species. Preferably, the polypeptide is encoded by a polynucleotide sequence disclosed herein or a sequence which hybridizes under moderately stringent conditions to a polynucleotide sequence disclosed herein. Alternatively, the polypeptide may be defined as a polypeptide which comprises a contiguous amino acid sequence from an amino acid sequence disclosed herein, or which polypeptide comprises an entire amino acid sequence disclosed herein.

In the present invention, a polypeptide composition is also understood to comprise one or more polypeptides that are immunologically reactive with antibodies generated against a polypeptide of the invention, particularly a polypeptide having the amino acid sequence disclosed in SEQ ID NO: 391 and 393, or to active fragments, or to variants or biological functional equivalents thereof.

Likewise, a polypeptide composition of the present invention is understood to comprise one or more polypeptides that are capable of eliciting antibodies that are

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immunologically reactive with one or more polypeptides encoded by one or more contiguous nucleic acid sequences contained in SEQ ID NO: 217-390 and 392, or to active fragments, or to variants thereof, or to one or more nucleic acid sequences which hybridize to one or more of these sequences under conditions of moderate to high stringency. Particularly illustrative polypeptides include the amino acid sequence disclosed in SEQ ID NO:391, 393, 395, 397, 421 and 425-427.

As used herein, an active fragment of a polypeptide includes a whole or a portion of a polypeptide which is modified by conventional techniques, *e.g.*, mutagenesis, or by addition, deletion, or substitution, but which active fragment exhibits substantially the same structure function, antigenicity, etc., as a polypeptide as described herein.

In certain illustrative embodiments, the polypeptides of the invention will comprise at least an immunogenic portion of a lung tumor protein or a variant thereof, as described herein. As noted above, a "lung tumor protein" is a protein that is expressed by lung tumor cells. Proteins that are lung tumor proteins also react detectably within an immunoassay (such as an ELISA) with antisera from a patient with lung cancer. Polypeptides as described herein may be of any length. Additional sequences derived from the native protein and/or heterologous sequences may be present, and such sequences may (but need not) possess further immunogenic or antigenic properties.

An "immunogenic portion," as used herein is a portion of a protein that is recognized (*i.e.*, specifically bound) by a B-cell and/or T-cell surface antigen receptor. Such immunogenic portions generally comprise at least 5 amino acid residues, more preferably at least 10, and still more preferably at least 20 amino acid residues of a lung tumor protein or a variant thereof. Certain preferred immunogenic portions include peptides in which an N-terminal leader sequence and/or transmembrane domain have been deleted. Other preferred immunogenic portions may contain a small N- and/or C-terminal deletion (*e.g.*, 1-30 amino acids, preferably 5-15 amino acids), relative to the mature protein.

Immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, *Fundamental Immunology*, 3rd ed., 243-247

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(Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with antigen-specific antibodies, antisera and/or T-cell lines or clones. As used herein, antisera and antibodies are "antigen-specific" if they specifically bind to an antigen (i.e., they react with the protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera and antibodies may be prepared as described herein, and using well known techniques. An immunogenic portion of a native lung tumor protein is a portion that reacts with such antisera and/or T-cells at a level that is not substantially less than the reactivity of the full length polypeptide (e.g., in an ELISA and/or T-cell reactivity assay). Such immunogenic portions may react within such assays at a level that is similar to or greater than the reactivity of the full length polypeptide. Such screens may generally be performed using methods well known to those of ordinary skill in the art, such as those described in Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. For example, a polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, <sup>125</sup>I-labeled Protein A.

As noted above, a composition may comprise a variant of a native lung tumor protein. A polypeptide "variant," as used herein, is a polypeptide that differs from a native lung tumor protein in one or more substitutions, deletions, additions and/or insertions, such that the immunogenicity of the polypeptide is not substantially diminished. In other words, the ability of a variant to react with antigen-specific antisera may be enhanced or unchanged, relative to the native protein, or may be diminished by less than 50%, and preferably less than 20%, relative to the native protein. Such variants may generally be identified by modifying one of the above polypeptide sequences and evaluating the reactivity of the modified polypeptide with antigen-specific antibodies or antisera as described herein. Preferred variants include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other preferred variants include variants in which a small portion (e.g., 1-30)

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amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein.

Polypeptide variants encompassed by the present invention include those exhibiting at least about 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% or more identity (determined as described above) to the polypeptides disclosed herein.

Preferably, a variant contains conservative substitutions. A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. Amino acid substitutions may generally be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain nonconservative changes. In a preferred embodiment, variant polypeptides differ from a native sequence by substitution, deletion or addition of five amino acids or fewer. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydropathic nature of the polypeptide.

As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein, which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (e.g., poly-

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His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

Polypeptides may be prepared using any of a variety of well known techniques. Recombinant polypeptides encoded by DNA sequences as described above may be readily prepared from the DNA sequences using any of a variety of expression vectors known to those of ordinary skill in the art. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast, and higher eukaryotic cells, such as mammalian cells and plant cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line such as COS or CHO. Supernatants from suitable host/vector systems which secrete recombinant protein or polypeptide into culture media may be first concentrated using a commercially available filter. Following concentration, the concentrate may be applied to a suitable purification matrix such as an affinity matrix or an ion exchange resin. Finally, one or more reverse phase HPLC steps can be employed to further purify a recombinant polypeptide.

Portions and other variants having less than about 100 amino acids, and generally less than about 50 amino acids, may also be generated by synthetic means, using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. *See* Merrifield, *J. Am. Chem. Soc.* 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

Within certain specific embodiments, a polypeptide may be a fusion protein that comprises multiple polypeptides as described herein, or that comprises at least one polypeptide as described herein and an unrelated sequence, such as a known tumor protein. A fusion partner may, for example, assist in providing T helper epitopes (an immunological

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fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the protein or to enable the protein to be targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the protein.

Fusion proteins may generally be prepared using standard techniques, including chemical conjugation. Preferably, a fusion protein is expressed as a recombinant protein, allowing the production of increased levels, relative to a non-fused protein, in an expression system. Briefly, DNA sequences encoding the polypeptide components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase. This permits translation into a single fusion protein that retains the biological activity of both component polypeptides.

A peptide linker sequence may be employed to separate the first and second polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea *et al.*, *Gene 40*:39-46, 1985; Murphy *et al.*, *Proc. Natl. Acad. Sci. USA 83*:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may

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generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

Fusion proteins are also provided. Such proteins comprise a polypeptide as described herein together with an unrelated immunogenic protein. Preferably the immunogenic protein is capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (see, for example, Stoute et al. New Engl. J. Med., 336:86-91, 1997).

Within preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium Haemophilus influenza B (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (e.g., the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in E. coli (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen presenting cells. Other fusion partners include the non-structural protein from influenzae virus, NS1 (hemaglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine amidase known as amidase LYTA (encoded by the LytA gene; *Gene 43*:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-

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terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been exploited for the development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (*see Biotechnology 10*:795-798, 1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion protein. A repeat portion is found in the C-terminal region starting at residue 178. A particularly preferred repeat portion incorporates residues 188-305.

In general, polypeptides (including fusion proteins) and polynucleotides as described herein are isolated. An "isolated" polypeptide or polynucleotide is one that is removed from its original environment. For example, a naturally-occurring protein is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure. A polynucleotide is considered to be isolated if, for example, it is cloned into a vector that is not a part of the natural environment.

#### **BINDING AGENTS**

The present invention further provides agents, such as antibodies and antigen-binding fragments thereof, that specifically bind to a lung tumor protein. As used herein, an antibody, or antigen-binding fragment thereof, is said to "specifically bind" to a lung tumor protein if it reacts at a detectable level (within, for example, an ELISA) with a lung tumor protein, and does not react detectably with unrelated proteins under similar conditions. As used herein, "binding" refers to a noncovalent association between two separate molecules such that a complex is formed. The ability to bind may be evaluated by, for example, determining a binding constant for the formation of the complex. The binding constant is the value obtained when the concentration of the complex is divided by the product of the component concentrations. In general, two compounds are said to "bind," in the context of the present invention, when the binding constant for complex

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formation exceeds about 10<sup>3</sup> L/mol. The binding constant may be determined using methods well known in the art.

Binding agents may be further capable of differentiating between patients with and without a cancer, such as lung cancer, using the representative assays provided herein. In other words, antibodies or other binding agents that bind to a lung tumor protein will generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, and will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies this requirement, biological samples (e.g., blood, sera, sputum, urine and/or tumor biopsies) from patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. It will be apparent that a statistically significant number of samples with and without the disease should be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. *See, e.g.,* Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation of monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (*e.g.,* mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as

bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol.* 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (*i.e.*, reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

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Within certain embodiments, the use of antigen-binding fragments of antibodies may be preferred. Such fragments include Fab fragments, which may be prepared using standard techniques. Briefly, immunoglobulins may be purified from rabbit serum by affinity chromatography on Protein A bead columns (Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988) and digested by papain to yield Fab and Fc fragments. The Fab and Fc fragments may be separated by affinity chromatography on protein A bead columns.

Monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include <sup>90</sup>Y, <sup>123</sup>I, <sup>125</sup>I, <sup>131</sup>I, <sup>186</sup>Re, <sup>188</sup>Re, <sup>211</sup>At, and <sup>212</sup>Bi. Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diptheria toxin, cholera toxin, gelonin, Pseudomonas exotoxin, Shigella toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (e.g., covalently bonded) to a suitable monoclonal antibody either directly or indirectly (e.g., via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (e.g., a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

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It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, *e.g.*, U.S. Patent No. 4,671,958, to Rodwell *et al.* 

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (e.g., U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (e.g., U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of derivatized amino acid side chains (e.g., U.S. Patent No. 4,638,045, to Kohn et al.), by serum complement-mediated hydrolysis (e.g., U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (e.g., U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers that provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (e.g., U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (e.g., U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (e.g., U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide

agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison *et al.* discloses representative chelating compounds and their synthesis.

A variety of routes of administration for the antibodies and immunoconjugates may be used. Typically, administration will be intravenous, intramuscular, subcutaneous or in the bed of a resected tumor. It will be evident that the precise dose of the antibody/immunoconjugate will vary depending upon the antibody used, the antigen density on the tumor, and the rate of clearance of the antibody.

### T CELLS

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Immunotherapeutic compositions may also, or alternatively, comprise T cells specific for a lung tumor protein. Such cells may generally be prepared *in vitro* or *ex vivo*, using standard procedures. For example, T cells may be isolated from bone marrow, peripheral blood, or a fraction of bone marrow or peripheral blood of a patient, using a commercially available cell separation system, such as the Isolex<sup>TM</sup> System, available from Nexell Therapeutics, Inc. (Irvine, CA; see also U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). Alternatively, T cells may be derived from related or unrelated humans, non-human mammals, cell lines or cultures.

T cells may be stimulated with a lung tumor polypeptide, polynucleotide encoding a lung tumor polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide. Preferably, a lung tumor polypeptide or polynucleotide is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

T cells are considered to be specific for a lung tumor polypeptide if the T cells specifically proliferate, secrete cytokines or kill target cells coated with the

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polypeptide or expressing a gene encoding the polypeptide. T cell specificity may be evaluated using any of a variety of standard techniques. For example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen et al., Cancer Res. 54:1065-1070, 1994. Alternatively, detection of the proliferation of T cells may be accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (e.g., by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with a lung tumor polypeptide (100 ng/ml - 100 µg/ml, preferably 200 ng/ml - 25 μg/ml) for 3 - 7 days should result in at least a two fold increase in proliferation of the T cells. Contact as described above for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (e.g., TNF or IFN-y) is indicative of T cell activation (see Coligan et al., Current Protocols in Immunology, vol. 1, Wiley Interscience (Greene 1998)). T cells that have been activated in response to a lung tumor polypeptide, polynucleotide or polypeptide-expressing APC may be CD4<sup>+</sup> and/or CD8<sup>+</sup>. Lung tumor protein-specific T cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from a patient, a related donor or an unrelated donor, and are administered to the patient following stimulation and expansion.

For therapeutic purposes, CD4<sup>+</sup> or CD8<sup>+</sup> T cells that proliferate in response to a lung tumor polypeptide, polynucleotide or APC can be expanded in number either *in vitro* or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a variety of ways. For example, the T cells can be re-exposed to a lung tumor polypeptide, or a short peptide corresponding to an immunogenic portion of such a polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize a lung tumor polypeptide. Alternatively, one or more T cells that proliferate in the presence of a lung tumor protein can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution.

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### PHARMACEUTICAL COMPOSITIONS

In additional embodiments, the present invention concerns formulation of one or more of the polynucleotide, polypeptide, T-cell and/or antibody compositions disclosed herein in pharmaceutically-acceptable solutions for administration to a cell or an animal, either alone, or in combination with one or more other modalities of therapy.

It will also be understood that, if desired, the nucleic acid segment, RNA, DNA or PNA compositions that express a polypeptide as disclosed herein may be administered in combination with other agents as well, such as, e.g., other proteins or polypeptides or various pharmaceutically-active agents. In fact, there is virtually no limit to other components that may also be included, given that the additional agents do not cause a significant adverse effect upon contact with the target cells or host tissues. The compositions may thus be delivered along with various other agents as required in the particular instance. Such compositions may be purified from host cells or other biological sources, or alternatively may be chemically synthesized as described herein. Likewise, such compositions may further comprise substituted or derivatized RNA or DNA compositions.

Formulation of pharmaceutically-acceptable excipients and carrier solutions is well-known to those of skill in the art, as is the development of suitable dosing and treatment regimens for using the particular compositions described herein in a variety of treatment regimens, including *e.g.*, oral, parenteral, intravenous, intranasal, and intramuscular administration and formulation.

# 1. ORAL DELIVERY

In certain applications, the pharmaceutical compositions disclosed herein may be delivered *via* oral administration to an animal. As such, these compositions may be formulated with an inert diluent or with an assimilable edible carrier, or they may be enclosed in hard- or soft-shell gelatin capsule, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet.

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The active compounds may even be incorporated with excipients and used in the form of ingestible tablets, buccal tables, troches, capsules, elixirs, suspensions, syrups, wafers, and the like (Mathiowitz et al., 1997; Hwang et al., 1998; U. S. Patent 5,641,515; U. S. Patent 5,580,579 and U. S. Patent 5,792,451, each specifically incorporated herein by reference in its entirety). The tablets, troches, pills, capsules and the like may also contain the following: a binder, as gum tragacanth, acacia, cornstarch, or gelatin; excipients, such as dicalcium phosphate; a disintegrating agent, such as corn starch, potato starch, alginic acid and the like; a lubricant, such as magnesium stearate; and a sweetening agent, such as sucrose, lactose or saccharin may be added or a flavoring agent, such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar, or both. A syrup of elixir may contain the active compound sucrose as a sweetening agent methyl and propylparabens as preservatives, a dye and flavoring, such as cherry or orange Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compounds may be incorporated into sustained-release preparation and formulations.

Typically, these formulations may contain at least about 0.1% of the active compound or more, although the percentage of the active ingredient(s) may, of course, be varied and may conveniently be between about 1 or 2% and about 60% or 70% or more of the weight or volume of the total formulation. Naturally, the amount of active compound(s) in each therapeutically useful composition may be prepared is such a way that a suitable dosage will be obtained in any given unit dose of the compound. Factors such as solubility, bioavailability, biological half-life, route of administration, product shelf life, as well as other pharmacological considerations will be contemplated by one skilled in the art of preparing such pharmaceutical formulations, and as such, a variety of dosages and treatment regimens may be desirable.

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For oral administration the compositions of the present invention may alternatively be incorporated with one or more excipients in the form of a mouthwash, dentifrice, buccal tablet, oral spray, or sublingual orally-administered formulation. For example, a mouthwash may be prepared incorporating the active ingredient in the required amount in an appropriate solvent, such as a sodium borate solution (Dobell's Solution). Alternatively, the active ingredient may be incorporated into an oral solution such as one containing sodium borate, glycerin and potassium bicarbonate, or dispersed in a dentifrice, or added in a therapeutically-effective amount to a composition that may include water, binders, abrasives, flavoring agents, foaming agents, and humectants. Alternatively the compositions may be fashioned into a tablet or solution form that may be placed under the tongue or otherwise dissolved in the mouth.

### 2. INJECTABLE DELIVERY

In certain circumstances it will be desirable to deliver the pharmaceutical compositions disclosed herein parenterally, intravenously, intramuscularly, or even intraperitoneally as described in U. S. Patent 5,543,158; U. S. Patent 5,641,515 and U. S. Patent 5,399,363 (each specifically incorporated herein by reference in its entirety). Solutions of the active compounds as free base or pharmacologically acceptable salts may be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions may also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions (U. S. Patent 5,466,468, specifically incorporated herein by reference in its entirety). In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing,

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for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and/or vegetable oils. Proper fluidity may be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be facilitated by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

For parenteral administration in an aqueous solution, for example, the solution should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, a sterile aqueous medium that can be employed will be known to those of skill in the art in light of the present disclosure. For example, one dosage may be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml of hypodermoclysis fluid or injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences" 15th Edition, pages 1035-1038 and 1570-1580). Some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject. Moreover, for human administration, preparations should meet sterility, pyrogenicity, and the general safety and purity standards as required by FDA Office of Biologics standards.

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other

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ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

The compositions disclosed herein may be formulated in a neutral or salt form. Pharmaceutically-acceptable salts, include the acid addition salts (formed with the free amino groups of the protein) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like. Upon formulation, solutions will be administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective. The formulations are easily administered in a variety of dosage forms such as injectable solutions, drug-release capsules, and the like.

As used herein, "carrier" includes any and all solvents, dispersion media, vehicles, coatings, diluents, antibacterial and antifungal agents, isotonic and absorption delaying agents, buffers, carrier solutions, suspensions, colloids, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

The phrase "pharmaceutically-acceptable" refers to molecular entities and compositions that do not produce an allergic or similar untoward reaction when administered to a human. The preparation of an aqueous composition that contains a protein as an active ingredient is well understood in the art. Typically, such compositions are prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid prior to injection can also be prepared. The preparation can also be emulsified.

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### 3. NASAL DELIVERY

In certain embodiments, the pharmaceutical compositions may be delivered by intranasal sprays, inhalation, and/or other aerosol delivery vehicles. Methods for delivering genes, nucleic acids, and peptide compositions directly to the lungs *via* nasal aerosol sprays has been described *e.g.*, in U. S. Patent 5,756,353 and U. S. Patent 5,804,212 (each specifically incorporated herein by reference in its entirety). Likewise, the delivery of drugs using intranasal microparticle resins (Takenaga *et al.*, 1998) and lysophosphatidylglycerol compounds (U. S. Patent 5,725,871, specifically incorporated herein by reference in its entirety) are also well-known in the pharmaceutical arts. Likewise, transmucosal drug delivery in the form of a polytetrafluoroetheylene support matrix is described in U. S. Patent 5,780,045 (specifically incorporated herein by reference in its entirety).

## 4. LIPOSOME-, NANOCAPSULE-, AND MICROPARTICLE-MEDIATED DELIVERY

In certain embodiments, the inventors contemplate the use of liposomes, nanocapsules, microparticles, microspheres, lipid particles, vesicles, and the like, for the introduction of the compositions of the present invention into suitable host cells. In particular, the compositions of the present invention may be formulated for delivery either encapsulated in a lipid particle, a liposome, a vesicle, a nanosphere, or a nanoparticle or the like.

Such formulations may be preferred for the introduction of pharmaceutically-acceptable formulations of the nucleic acids or constructs disclosed herein. The formation and use of liposomes is generally known to those of skill in the art (see for example, Couvreur *et al.*, 1977; Couvreur, 1988; Lasic, 1998; which describes the use of liposomes and nanocapsules in the targeted antibiotic therapy for intracellular bacterial infections and diseases). Recently, liposomes were developed with improved serum stability and circulation half-times (Gabizon and Papahadjopoulos, 1988; Allen and Choun, 1987; U. S. Patent 5,741,516, specifically incorporated herein by reference in its entirety). Further, various methods of liposome and liposome like preparations as potential drug carriers have been reviewed (Takakura, 1998; Chandran *et al.*, 1997; Margalit, 1995;

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U. S. Patent 5,567,434; U. S. Patent 5,552,157; U. S. Patent 5,565,213; U. S. Patent 5,738,868 and U. S. Patent 5,795,587, each specifically incorporated herein by reference in its entirety).

Liposomes have been used successfully with a number of cell types that are normally resistant to transfection by other procedures including T cell suspensions, primary hepatocyte cultures and PC 12 cells (Renneisen *et al.*, 1990; Muller *et al.*, 1990). In addition, liposomes are free of the DNA length constraints that are typical of viral-based delivery systems. Liposomes have been used effectively to introduce genes, drugs (Heath and Martin, 1986; Heath *et al.*, 1986; Balazsovits *et al.*, 1989; Fresta and Puglisi, 1996), radiotherapeutic agents (Pikul *et al.*, 1987), enzymes (Imaizumi *et al.*, 1990a; Imaizumi *et al.*, 1990b), viruses (Faller and Baltimore, 1984), transcription factors and allosteric effectors (Nicolau and Gersonde, 1979) into a variety of cultured cell lines and animals. In addition, several successful clinical trails examining the effectiveness of liposomemediated drug delivery have been completed (Lopez-Berestein *et al.*, 1985a; 1985b; Coune, 1988; Sculier *et al.*, 1988). Furthermore, several studies suggest that the use of liposomes is not associated with autoimmune responses, toxicity or gonadal localization after systemic delivery (Mori and Fukatsu, 1992).

Liposomes are formed from phospholipids that are dispersed in an aqueous medium and spontaneously form multilamellar concentric bilayer vesicles (also termed multilamellar vesicles (MLVs). MLVs generally have diameters of from 25 nm to 4  $\mu$ m. Sonication of MLVs results in the formation of small unilamellar vesicles (SUVs) with diameters in the range of 200 to 500 Å, containing an aqueous solution in the core.

Liposomes bear resemblance to cellular membranes and are contemplated for use in connection with the present invention as carriers for the peptide compositions. They are widely suitable as both water- and lipid-soluble substances can be entrapped, *i.e.* in the aqueous spaces and within the bilayer itself, respectively. It is possible that the drugbearing liposomes may even be employed for site-specific delivery of active agents by selectively modifying the liposomal formulation.

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In addition to the teachings of Couvreur *et al.* (1977; 1988), the following information may be utilized in generating liposomal formulations. Phospholipids can form a variety of structures other than liposomes when dispersed in water, depending on the molar ratio of lipid to water. At low ratios the liposome is the preferred structure. The physical characteristics of liposomes depend on pH, ionic strength and the presence of divalent cations. Liposomes can show low permeability to ionic and polar substances, but at elevated temperatures undergo a phase transition which markedly alters their permeability. The phase transition involves a change from a closely packed, ordered structure, known as the gel state, to a loosely packed, less-ordered structure, known as the fluid state. This occurs at a characteristic phase-transition temperature and results in an increase in permeability to ions, sugars and drugs.

In addition to temperature, exposure to proteins can alter the permeability of liposomes. Certain soluble proteins, such as cytochrome c, bind, deform and penetrate the bilayer, thereby causing changes in permeability. Cholesterol inhibits this penetration of proteins, apparently by packing the phospholipids more tightly. It is contemplated that the most useful liposome formations for antibiotic and inhibitor delivery will contain cholesterol.

The ability to trap solutes varies between different types of liposomes. For example, MLVs are moderately efficient at trapping solutes, but SUVs are extremely inefficient. SUVs offer the advantage of homogeneity and reproducibility in size distribution, however, and a compromise between size and trapping efficiency is offered by large unilamellar vesicles (LUVs). These are prepared by ether evaporation and are three to four times more efficient at solute entrapment than MLVs.

In addition to liposome characteristics, an important determinant in entrapping compounds is the physicochemical properties of the compound itself. Polar compounds are trapped in the aqueous spaces and nonpolar compounds bind to the lipid bilayer of the vesicle. Polar compounds are released through permeation or when the bilayer is broken, but nonpolar compounds remain affiliated with the bilayer unless it is

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disrupted by temperature or exposure to lipoproteins. Both types show maximum efflux rates at the phase transition temperature.

Liposomes interact with cells *via* four different mechanisms: endocytosis by phagocytic cells of the reticuloendothelial system such as macrophages and neutrophils; adsorption to the cell surface, either by nonspecific weak hydrophobic or electrostatic forces, or by specific interactions with cell-surface components; fusion with the plasma cell membrane by insertion of the lipid bilayer of the liposome into the plasma membrane, with simultaneous release of liposomal contents into the cytoplasm; and by transfer of liposomal lipids to cellular or subcellular membranes, or vice versa, without any association of the liposome contents. It often is difficult to determine which mechanism is operative and more than one may operate at the same time.

The fate and disposition of intravenously injected liposomes depend on their physical properties, such as size, fluidity, and surface charge. They may persist in tissues for h or days, depending on their composition, and half lives in the blood range from min to several h. Larger liposomes, such as MLVs and LUVs, are taken up rapidly by phagocytic cells of the reticuloendothelial system, but physiology of the circulatory system restrains the exit of such large species at most sites. They can exit only in places where large openings or pores exist in the capillary endothelium, such as the sinusoids of the liver or spleen. Thus, these organs are the predominate site of uptake. On the other hand, SUVs show a broader tissue distribution but still are sequestered highly in the liver and spleen. In general, this *in vivo* behavior limits the potential targeting of liposomes to only those organs and tissues accessible to their large size. These include the blood, liver, spleen, bone marrow, and lymphoid organs.

Targeting is generally not a limitation in terms of the present invention. However, should specific targeting be desired, methods are available for this to be accomplished. Antibodies may be used to bind to the liposome surface and to direct the antibody and its drug contents to specific antigenic receptors located on a particular cell-type surface. Carbohydrate determinants (glycoprotein or glycolipid cell-surface components that play a role in cell-cell recognition, interaction and adhesion) may also be

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used as recognition sites as they have potential in directing liposomes to particular cell types. Mostly, it is contemplated that intravenous injection of liposomal preparations would be used, but other routes of administration are also conceivable.

Alternatively, the invention provides for pharmaceutically-acceptable nanocapsule formulations of the compositions of the present invention. Nanocapsules can generally entrap compounds in a stable and reproducible way (Henry-Michelland *et al.*, 1987; Quintanar-Guerrero *et al.*, 1998; Douglas *et al.*, 1987). To avoid side effects due to intracellular polymeric overloading, such ultrafine particles (sized around 0.1 µm) should be designed using polymers able to be degraded *in vivo*. Biodegradable polyalkyl-cyanoacrylate nanoparticles that meet these requirements are contemplated for use in the present invention. Such particles may be are easily made, as described (Couvreur *et al.*, 1980; 1988; zur Muhlen *et al.*, 1998; Zambaux *et al.* 1998; Pinto-Alphandry *et al.*, 1995 and U. S. Patent 5,145,684, specifically incorporated herein by reference in its entirety).

### **IMMUNOGENIC COMPOSITIONS**

In certain preferred embodiments of the present invention, immunogenic compositions, or vaccines, are provided. The immunogenic compositions will generally comprise one or more pharmaceutical compositions, such as those discussed above, in combination with an immunostimulant. An immunostimulant may be any substance that enhances or potentiates an immune response (antibody and/or cell-mediated) to an exogenous antigen. Examples of immunostimulants include adjuvants, biodegradable microspheres (e.g., polylactic galactide) and liposomes (into which the compound is incorporated; see e.g., Fullerton, U.S. Patent No. 4,235,877). Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Pharmaceutical compositions and immunogenic compositions within the scope of the present invention may also contain other compounds, which may be biologically active or inactive. For example, one or more immunogenic portions of other tumor antigens may be present, either incorporated into a fusion polypeptide or as a separate compound, within the composition.

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Illustrative immunogenic compositions may contain DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated in situ. As noted above, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacteria and viral expression systems. Numerous gene delivery techniques are well known in the art, such as those described by Rolland, Crit. Rev. Therap. Drug Carrier Systems 15:143-198, 1998, and references cited therein. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a Bacterial delivery systems involve the suitable promoter and terminating signal). administration of a bacterium (such as Bacillus-Calmette-Guerrin) that expresses an immunogenic portion of the polypeptide on its cell surface or secretes such an epitope. In a preferred embodiment, the DNA may be introduced using a viral expression system (e.g., vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a nonpathogenic (defective), replication competent virus. Suitable systems are disclosed, for example, in Fisher-Hoch et al., Proc. Natl. Acad. Sci. USA 86:317-321, 1989; Flexner et al., Ann. N.Y. Acad. Sci. 569:86-103, 1989; Flexner et al., Vaccine 8:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, Biotechniques 6:616-627, 1988; Rosenfeld et al., Science 252:431-434, 1991; Kolls et al., Proc. Natl. Acad. Sci. USA 91:215-219, 1994; Kass-Eisler et al., Proc. Natl. Acad. Sci. USA 90:11498-11502, 1993; Guzman et al., Circulation 88:2838-2848, 1993; and Guzman et al., Cir. Res. 73:1202-1207, 1993. Techniques for incorporating DNA into such expression systems are well known to those of ordinary skill in the art. The DNA may also be "naked," as described, for example, in Ulmer et al., Science 259:1745-1749, 1993 and reviewed by Cohen, Science 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells. It will be apparent that an immunogenic composition may comprise both a polynucleotide and a polypeptide component. Such immunogenic compositions may provide for an enhanced immune response.

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It will be apparent that an immunogenic composition may contain pharmaceutically acceptable salts of the polynucleotides and polypeptides provided herein. Such salts may be prepared from pharmaceutically acceptable non-toxic bases, including organic bases (e.g., salts of primary, secondary and tertiary amines and basic amino acids) and inorganic bases (e.g., sodium, potassium, lithium, ammonium, calcium and magnesium salts).

While any suitable carrier known to those of ordinary skill in the art may be employed in the compositions of this invention, the type of carrier will vary depending on the mode of administration. Compositions of the present invention may be formulated for any appropriate manner of administration, including for example, topical, oral, nasal, intravenous, intracranial, intraperitoneal, subcutaneous or intramuscular administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a fat, a wax or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and magnesium carbonate, may be Biodegradable microspheres (e.g., polylactate polyglycolate) may also be employed as carriers for the pharmaceutical compositions of this invention. biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268; 5,075,109; 5,928,647; 5,811,128; 5,820,883; 5,853,763; 5,814,344 and 5,942,252. may also employ a carrier comprising the particulate-protein complexes described in U.S. Patent No. 5,928,647, which are capable of inducing a class I-restricted cytotoxic T lymphocyte responses in a host.

Such compositions may also comprise buffers (e.g., neutral buffered saline or phosphate buffered saline), carbohydrates (e.g., glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, bacteriostats, chelating agents such as EDTA or glutathione, adjuvants (e.g., aluminum hydroxide), solutes that render the formulation isotonic, hypotonic or weakly hypertonic with the blood of a recipient, suspending agents, thickening agents and/or preservatives. Alternatively,

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compositions of the present invention may be formulated as a lyophilizate. Compounds may also be encapsulated within liposomes using well known technology.

Any of a variety of immunostimulants may be employed in the immunogenic compositions of this invention. For example, an adjuvant may be included. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune responses, such as lipid A, *Bortadella pertussis* or *Mycobacterium tuberculosis* derived proteins. Suitable adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI); Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ); AS-2 (SmithKline Beecham, Philadelphia, PA); aluminum salts such as aluminum hydroxide gel (alum) or aluminum phosphate; salts of calcium, iron or zinc; an insoluble suspension of acylated tyrosine; acylated sugars; cationically or anionically derivatized polysaccharides; polyphosphazenes; biodegradable microspheres; monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF or interleukin-2, -7, or -12, may also be used as adjuvants.

Within the immunogenic compositions provided herein, the adjuvant composition is preferably designed to induce an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (e.g., IFN-γ, TNFα, IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (e.g., IL-4, IL-5, IL-6 and IL-10) tend to favor the induction of humoral immune responses. Following application of an immunogenic composition as provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman, Ann. Rev. Immunol. 7:145-173, 1989.

Preferred adjuvants for use in eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-

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acylated monophosphoryl lipid A (3D-MPL), together with an aluminum salt. MPL adjuvants are available from Corixa Corporation (Seattle, WA; see US Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555, WO 99/33488 and U.S. Patent Nos. 6,008,200 and 5,856,462. Immunostimulatory DNA sequences are also described, for example, by Sato et al., Science 273:352, 1996. Another preferred adjuvant is a saponin, preferably QS21 (Aquila Biopharmaceuticals Inc., Framingham, MA), which may be used alone or in combination with other adjuvants. For example, an enhanced system involves the combination of a monophosphoryl lipid A and saponin derivative, such as the combination of QS21 and 3D-MPL as described in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol, as described in WO 96/33739. Other preferred formulations comprise an oil-in-water emulsion and tocopherol. A particularly potent adjuvant formulation involving QS21, 3D-MPL and tocopherol in an oil-in-water emulsion is described in WO 95/17210.

Other preferred adjuvants include Montanide ISA 720 (Seppic, France), SAF (Chiron, California, United States), ISCOMS (CSL), MF-59 (Chiron), the SBAS series of adjuvants (*e.g.*, SBAS-2 or SBAS-4, available from SmithKline Beecham, Rixensart, Belgium), Detox (Corixa, Hamilton, MT), RC-529 (Corixa, Hamilton, MT) and other aminoalkyl glucosaminide 4-phosphates (AGPs), such as those described in pending U.S. Patent Application Serial Nos. 08/853,826 and 09/074,720, the disclosures of which are incorporated herein by reference in their entireties.

Any immunogenic composition provided herein may be prepared using well known methods that result in a combination of antigen, immune response enhancer and a suitable carrier or excipient. The compositions described herein may be administered as part of a sustained release formulation (*i.e.*, a formulation such as a capsule, sponge or gel (composed of polysaccharides, for example) that effects a slow release of compound following administration). Such formulations may generally be prepared using well known technology (*see*, *e.g.*, Coombes *et al.*, *Vaccine 14*:1429-1438, 1996) and administered by,

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for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain a polypeptide, polynucleotide or antibody dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane.

Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of active component release. Such carriers include microparticles of poly(lactide-co-glycolide), polyacrylate, latex, starch, cellulose, dextran and the like. Other delayed-release carriers include supramolecular biovectors, which comprise a non-liquid hydrophilic core (e.g., a cross-linked polysaccharide or oligosaccharide) and, optionally, an external layer comprising an amphiphilic compound, such as a phospholipid (see e.g., U.S. Patent No. 5,151,254 and PCT applications WO 94/20078, WO/94/23701 and WO 96/06638). The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Any of a variety of delivery vehicles may be employed within pharmaceutical compositions and immunogenic compositions to facilitate production of an antigen-specific immune response that targets tumor cells. Delivery vehicles include antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or maintenance of the T cell response, to have anti-tumor effects *per se* and/or to be immunologically compatible with the receiver (*i.e.*, matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature 392*:245-251, 1998) and have been shown to be

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effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (see Timmerman and Levy, Ann. Rev. Med. 50:507-529, 1999). In general, dendritic cells may be identified based on their typical shape (stellate in situ, with marked cytoplasmic processes (dendrites) visible in vitro), their ability to take up, process and present antigens with high efficiency and their ability to activate naïve T cell responses. Dendritic cells may, of course, be engineered to express specific cell-surface receptors or ligands that are not commonly found on dendritic cells in vivo or ex vivo, and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within an immunogenic composition (see Zitvogel et al., Nature Med. 4:594-600, 1998).

Dendritic cells and progenitors may be obtained from peripheral blood, bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4, IL-13 and/or TNFα to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNFα, CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce differentiation, maturation and proliferation of dendritic cells.

Dendritic cells are conveniently categorized as "immature" and "mature" cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC with a high capacity for antigen uptake and processing, which correlates with the high expression of Fcγ receptor and mannose receptor. The mature phenotype is typically characterized by a lower expression of these markers, but a high expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion

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molecules (e.g., CD54 and CD11) and costimulatory molecules (e.g., CD40, CD80, CD86 and 4-1BB).

APCs may generally be transfected with a polynucleotide encoding a lung tumor protein (or portion or other variant thereof) such that the lung tumor polypeptide, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place ex vivo, and a composition comprising such transfected cells may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be administered to a patient, resulting in transfection that occurs in vivo. In vivo and ex vivo transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi et al., Immunology and cell Biology 75:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or progenitor cells with the lung tumor polypeptide, DNA (naked or within a plasmid vector) or RNA; or with antigen-expressing recombinant bacterium or viruses (e.g., vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently conjugated to an immunological partner that provides T cell help (e.g., a carrier molecule). Alternatively, a dendritic cell may be pulsed with a non-conjugated immunological partner, separately or in the presence of the polypeptide.

Immunogenic compositions and pharmaceutical compositions may be presented in unit-dose or multi-dose containers, such as sealed ampoules or vials. Such containers are preferably hermetically sealed to preserve sterility of the formulation until use. In general, formulations may be stored as suspensions, solutions or emulsions in oily or aqueous vehicles. Alternatively, a immunogenic composition or pharmaceutical composition may be stored in a freeze-dried condition requiring only the addition of a sterile liquid carrier immediately prior to use.

#### **CANCER THERAPY**

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In further aspects of the present invention, the compositions described herein may be used for immunotherapy of cancer, such as lung cancer. Within such methods, pharmaceutical compositions and immunogenic compositions are typically administered to a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions and immunogenic compositions may be used to prevent the development of a cancer or to treat a patient afflicted with a cancer. A cancer may be diagnosed using criteria generally accepted in the art, including the presence of a malignant tumor. Pharmaceutical compositions and immunogenic compositions may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or conventional chemotherapeutic drugs. Administration may be by any suitable method, including administration by intravenous, intraperitoneal, intramuscular, subcutaneous, intranasal, intradermal, anal, vaginal, topical and oral routes.

Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immune responsemodifying agents (such as polypeptides and polynucleotides as provided herein).

Within other embodiments. immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established tumorimmune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T cells as discussed above, T lymphocytes (such as CD8<sup>+</sup> cytotoxic T lymphocytes and CD4<sup>+</sup> T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-activated killer cells), B cells and antigen-presenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other

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vectors or effector cells for adoptive immunotherapy. The polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth in vitro, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition in vivo are well known in the art. Such in vitro culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast and/or B cells, may be pulsed with immunoreactive polypeptides or transfected with one or more polynucleotides using standard techniques well known in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system. Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term in vivo. Studies have shown that cultured effector cells can be induced to grow in vivo and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (see, for example, Cheever et al., Immunological Reviews 157:177, 1997).

Alternatively, a vector expressing a polypeptide recited herein may be introduced into antigen presenting cells taken from a patient and clonally propagated *ex vivo* for transplant back into the same patient. Transfected cells may be reintroduced into the patient using any means known in the art, preferably in sterile form by intravenous, intracavitary, intraperitoneal or intratumor administration.

Routes and frequency of administration of the therapeutic compositions described herein, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions

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and immunogenic compositions may be administered by injection (e.g., intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (e.g., by aspiration) or orally. Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (i.e., untreated) level. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccine-dependent generation of cytolytic effector cells capable of killing the patient's tumor cells in vitro. Such immunogenic compositions should also be capable of causing an immune response that leads to an improved clinical outcome (e.g., more frequent remissions, complete or partial or longer disease-free survival) in treated patients as compared to non-treated patients. In general, for pharmaceutical compositions and immunogenic compositions comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 25 µg to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (e.g., more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to a lung tumor protein generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

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#### **CANCER DETECTION AND DIAGNOSIS**

In general, a cancer may be detected in a patient based on the presence of one or more lung tumor proteins and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, sputum urine and/or tumor biopsies) obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as lung cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, a lung tumor sequence should be present at a level that is at least three fold higher in tumor tissue than in normal tissue

There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. See, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the

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labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include full length lung tumor proteins and portions thereof to which the binding agent binds, as described above.

The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 µg, and preferably about 100 ng to about 1 µg, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group

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on the support with an amine and an active hydrogen on the binding partner (see, e.g., Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20™ (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with lung cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20<sup>TM</sup>. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

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The detection reagent is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound detection reagent is then removed and bound detection reagent is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of a cancer, such as lung cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., Clinical Epidemiology: A Basic Science for Clinical Medicine, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (i.e., sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (i.e., the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the

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false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1µg, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use lung tumor polypeptides to detect antibodies that bind to such polypeptides in a biological sample.

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The detection of such lung tumor protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with a lung tumor protein in a biological sample. Within certain methods, a biological sample comprising CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells isolated from a patient is incubated with a lung tumor polypeptide, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated in vitro for 2-9 days (typically 4 days) at 37°C with polypeptide (e.g., 5 - 25 μg/ml). It may be desirable to incubate another aliquot of a T cell sample in the absence of lung tumor polypeptide to serve as a control. For CD4<sup>+</sup> T cells, activation is preferably detected by evaluating proliferation of the T cells. For CD8<sup>+</sup> T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding a lung tumor protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify a portion of a lung tumor cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the lung tumor protein. The amplified cDNA is then separated and detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding a lung tumor protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

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To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding a lung tumor protein that is at least 10 nucleotides, and preferably at least 20 nucleotides, in length. Preferably, oligonucleotide primers and/or probes hybridize to a polynucleotide encoding a polypeptide described herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence recited in SEQ ID NOs:217-390, 392, 394, 396, 398-420 and 422-424. Techniques for both PCR based assays and hybridization assays are well known in the art (see, for example, Mullis et al., Cold Spring Harbor Symp. Quant. Biol., 51:263, 1987; Erlich ed., PCR Technology, Stockton Press, NY, 1989).

One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample, such as biopsy tissue, and is reverse transcribed to produce cDNA molecules. PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an individual who is not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

In another embodiment, the compositions described herein may be used as markers for the progression of cancer. In this embodiment, assays as described above for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) or polynucleotide(s) evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed

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as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide or polynucleotide detected increases over time. In contrast, the cancer is not progressing when the level of reactive polypeptide or polynucleotide either remains constant or decreases with time.

Certain *in vivo* diagnostic assays may be performed directly on a tumor. One such assay involves contacting tumor cells with a binding agent. The bound binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple lung tumor protein markers may be assayed within a given sample. It will be apparent that binding agents specific for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein markers may be based on routine experiments to determine combinations that results in optimal sensitivity. In addition, or alternatively, assays for tumor proteins provided herein may be combined with assays for other known tumor antigens.

#### **DIAGNOSTIC KITS**

The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components necessary for performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to a lung tumor protein. Such antibodies or fragments may be provided attached to a support material, as described above. One or more additional containers may enclose elements, such as reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

Alternatively, a kit may be designed to detect the level of mRNA encoding a lung tumor protein in a biological sample. Such kits generally comprise at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding a lung tumor protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate the detection of a polynucleotide encoding a lung tumor protein.

The following Examples are offered by way of illustration and not by way of limitation.

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#### Example 1

## PREPARATION OF LUNG TUMOR-SPECIFIC CDNA SEQUENCES USING DIFFERENTIAL DISPLAY RT-PCR

This example illustrates the preparation of cDNA molecules encoding lung tumor-specific polypeptides using a differential display screen.

Tissue samples were prepared from lung tumor and normal tissue of a patient with lung cancer that was confirmed by pathology after removal of samples from the patient. Normal RNA and tumor RNA was extracted from the samples and mRNA was isolated and converted into cDNA using a (dT)<sub>12</sub>AG (SEQ ID NO: 47) anchored 3' primer. Differential display PCR was then executed using a randomly chosen primer (SEQ ID NO: 48). Amplification conditions were standard buffer containing 1.5 mM MgCl<sub>2</sub>, 20 pmol of primer, 500 pmol dNTP and 1 unit of Taq DNA polymerase (Perkin-Elmer, Branchburg, NJ). Forty cycles of amplification were performed using 94 °C denaturation for 30 seconds, 42 °C annealing for 1 minute and 72 °C extension for 30 seconds. Bands that were repeatedly observed to be specific to the RNA fingerprint pattern of the tumor were cut out of a silver stained gel, subcloned into the pGEM-T vector (Promega, Madison, WI) and sequenced. The isolated 3' sequences are provided in SEQ ID NO: 1-16.

Comparison of these sequences to those in the public databases using the BLASTN program, revealed no significant homologies to the sequences provided in SEQ ID NO: 1-11. To the best of the inventors' knowledge, none of the isolated DNA sequences have previously been shown to be expressed at a greater level in human lung tumor tissue than in normal lung tissue.

### Example 2

## USE OF PATIENT SERA TO IDENTIFY DNA SEQUENCES ENCODING LUNG TUMOR ANTIGENS

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This example illustrates the isolation of cDNA sequences encoding lung tumor antigens by expression screening of lung tumor samples with autologous patient sera.

A human lung tumor directional cDNA expression library was constructed employing the Lambda ZAP Express expression system (Stratagene, La Jolla, CA). Total RNA for the library was taken from a late SCID mouse passaged human squamous epithelial lung carcinoma and poly A+ RNA was isolated using the Message Maker kit (Gibco BRL, Gaithersburg, MD). The resulting library was screened using *E. coliabsorbed* autologous patient serum, as described in Sambrook et al., (*Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989), with the secondary antibody being goat anti-human IgG-A-M (H + L) conjugated with alkaline phosphatase, developed with NBT/BCIP (Gibco BRL). Positive plaques expressing immunoreactive antigens were purified. Phagemid from the plaques was rescued and the nucleotide sequences of the clones was determined.

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Fifteen clones were isolated, referred to hereinafter as LT86-1 – LT86-15. The isolated cDNA sequences for LT86-1 – LT86-8 and LT86-10 - LT86-15 are provided in SEQ ID NO: 17-24 and 26-31, respectively, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 32-39 and 41-46, respectively. The determined cDNA sequence for LT86-9 is provided in SEQ ID NO: 25, with the corresponding predicted amino acid sequences from the 3' and 5' ends being provided in SEQ ID NO: 40 and 65, respectively. These sequences were compared to those in the gene bank as described above. Clones LT86-3, LT86-6 – LT86-9, LT86-11 – LT86-13 and LT86-15 (SEQ ID NO: 19, 22-25, 27-29 and 31, respectively) were found to show some homology to previously identified expressed sequence tags (ESTs), with clones LT86-6,

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LT86-8, LT86-11, LT86-12 and LT86-15 appearing to be similar or identical to each other. Clone LT86-3 was found to show some homology with a human transcription repressor. Clones LT86-6, 8, 9, 11, 12 and 15 were found to show some homology to a yeast RNA Pol II transcription regulation mediator. Clone LT86-13 was found to show some homology with a *C. elegans* leucine aminopeptidase. Clone LT86-9 appears to contain two inserts, with the 5' sequence showing homology to the previously identified antisense sequence of interferon alpha-induced P27, and the 3' sequence being similar to LT86-6. Clone LT86-14 (SEQ ID NO: 30) was found to show some homology to the trithorax gene and has an "RGD" cell attachment sequence and a beta-Lactamase A site which functions in hydrolysis of penicillin. Clones LT86-1, LT86-2, LT86-4, LT86-5 and LT86-10 (SEQ ID NOS: 17, 18, 20, 21 and 26, respectively) were found to show homology to previously identified genes. A subsequently determined extended cDNA sequence for LT86-4 is provided in SEQ ID NO: 66, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 67.

Subsequent studies led to the isolation of five additional clones, referred to as LT86-20, LT86-21, LT86-22, LT86-26 and LT86-27. The determined 5' cDNA sequences for LT86-20, LT86-22, LT86-26 and LT86-27 are provided in SEQ ID NO: 68 and 70-72, respectively, with the determined 3' cDNA sequences for LT86-21 being provided in SEQ ID NO: 69. The corresponding predicted amino acid sequences for LT86-20, LT86-21, LT86-22, LT86-26 and LT86-27 are provided in SEQ ID NO: 73-77, respectively. LT86-22 and LT86-27 were found to be highly similar to each other. Comparison of these sequences to those in the gene bank as described above, revealed no significant homologies to LT86-22 and LT86-27. LT86-20, LT86-21 and LT86-26 were found to show homology to previously identified genes.

In further studies, a cDNA expression library was prepared using mRNA from a lung small cell carcinoma cell line in the lambda ZAP Express expression vector (Stratagene), and screened as described above, with a pool of two lung small cell carcinoma patient sera. The sera pool was adsorbed with *E. coli* lysate and human PBMC lysate was added to the serum to block antibody to proteins found in normal tissue.

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Seventy-three clones were isolated. The determined cDNA sequences of these clones are provided in SEQ ID NO: 290-362. The sequences of SEQ ID NO: 289-292, 294, 296-297, 300, 302, 303, 305, 307-315, 317-320, 322-325, 327-332, 334, 335, 338-341, 343-352, 354-358, 360 and 362 were found to show some homology to previously isolated genes. The sequences of SEQ ID NO: 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359 and 361 were found to show some homology to previously identified ESTs.

#### Example 3

## USE OF MOUSE ANTISERA TO IDENTIFY DNA SEQUENCES ENCODING LUNG TUMOR ANTIGENS

This example illustrates the isolation of cDNA sequences encoding lung tumor antigens by screening of lung tumor cDNA libraries with mouse anti-tumor sera.

A directional cDNA lung tumor expression library was prepared as described above in Example 2. Sera was obtained from SCID mice containing late passaged human squamous cell and adenocarcinoma tumors. These sera were pooled and injected into normal mice to produce anti-lung tumor serum. Approximately 200,000 PFUs were screened from the unamplified library using this antiserum. Using a goat anti-mouse IgG-A-M (H+L) alkaline phosphatase second antibody developed with NBT/BCIP (BRL Labs.), approximately 40 positive plaques were identified. Phage was purified and phagemid excised for 9 clones with inserts in a pBK-CMV vector for expression in prokaryotic or eukaryotic cells.

The determined cDNA sequences for 7 of the isolated clones (hereinafter referred to as L86S-3, L86S-12, L86S-16, L86S-25, L86S-36, L86S-40 and L86S-46) are provided in SEQ ID NO: 49-55, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 56-62, respectively. The 5' cDNA sequences for the remaining 2 clones (hereinafter referred to as L86S-30 and L86S-41) are provided in SEQ ID NO: 63 and 64. L86S-36 and L86S-46 were subsequently determined to represent the same gene. Comparison of these sequences with those in the public database as described

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above, revealed no significant homologies to clones L86S-30, L86S-36 and L86S-46 (SEQ ID NO: 63, 53 and 55, respectively). L86S-16 (SEQ ID NO: 51) was found to show some homology to an EST previously identified in fetal lung and germ cell tumor. The remaining clones were found to show at least some degree of homology to previously identified human genes. Subsequently determined extended cDNA sequences for L86S-12, L86S-36 and L86S-46 are provided in SEQ ID NO: 78-80, respectively, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 81-83.

Subsequent studies led to the determination of 5' cDNA sequences for an additional nine clones, referred to as L86S-6, L86S-11, L86S-14, L86S-29, L86S-34, L86S-39, L86S-47, L86S-49 and L86S-51 (SEQ ID NO: 84-92, respectively). The corresponding predicted amino acid sequences are provided in SEQ ID NO: 93-101, respectively. L86S-30, L86S-39 and L86S-47 were found to be similar to each other. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to L86S-14. L86S-29 was found to show some homology to a previously identified EST. L86S-6, L86S-11, L86S-34, L86S-39, L86S-47, L86S-49 and L86S-51 were found to show some homology to previously identified genes.

In further studies, a directional cDNA library was constructed using a Stratagene kit with a Lambda Zap Express vector. Total RNA for the library was isolated from two primary squamous lung tumors and poly A+RNA was isolated using an oligo dT column. Antiserum was developed in normal mice using a pool of sera from three SCID mice implanted with human squamous lung carcinomas. Approximately 700,000 PFUs were screened from the unamplified library with *E. coli* absorbed mouse anti-SCID tumor serum. Positive plaques were identified as described above. Phage was purified and phagemid excised for 180 clones with inserts in a pBK-CMV vector for expression in prokaryotic or eukaryotic cells.

The determined cDNA sequences for 23 of the isolated clones are provided in SEQ ID NO: 126-148. Comparison of these sequences with those in the public database as described above revealed no significant homologies to the sequences of SEO ID NO:

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139 and 143-148. The sequences of SEQ ID NO: 126-138 and 140-142 were found to show homology to previously identified human polynucleotide sequences.

### Example 4

# USE OF MOUSE ANTISERA TO SCREEN LUNG TUMOR LIBRARIES PREPARED FROM SCID MICE

This example illustrates the isolation of cDNA sequences encoding lung tumor antigens by screening of lung tumor cDNA libraries prepared from SCID mice with mouse anti-tumor sera.

A directional cDNA lung tumor expression library was prepared using a Stratagene kit with a Lambda Zap Express vector. Total RNA for the library was taken from a late passaged lung adenocarcinoma grown in SCID mice. Poly A+ RNA was isolated using a Message Maker Kit (Gibco BRL). Sera was obtained from two SCID mice implanted with lung adenocarcinomas. These sera were pooled and injected into normal mice to produce anti-lung tumor serum. Approximately 700,000 PFUs were screened from the unamplified library with *E. coli*-absorbed mouse anti-SCID tumor serum. Positive plaques were identified with a goat anti-mouse IgG-A-M (H+L) alkaline phosphatase second antibody developed with NBT/BCIP (Gibco BRL). Phage was purified and phagemid excised for 100 clones with insert in a pBK-CMV vector for expression in prokaryotic or eukaryotic cells.

The determined 5' cDNA sequences for 33 of the isolated clones are provided in SEQ ID NO: 149-181. The corresponding predicted amino acid sequences for SEQ ID NO: 149, 150, 152-154, 156-158 and 160-181 are provided in SEQ ID NO: 182, 183, 186, 188-193 and 194-215, respectively. The clone of SEQ ID NO: 151 (referred to as SAL-25) was found to contain two open reading frames (ORFs). The predicted amino acid sequences encoded by these ORFs are provided in SEQ ID NO: 184 and 185. The clone of SEQ ID NO: 153 (referred to as SAL-50) was found to contain two open reading frames encoding the predicted amino acid sequences of SEQ ID NO: 187 and 216.

Similarly, the clone of SEQ ID NO: 155 (referred to as SAL-66) was found to contain two open reading frames encoding the predicted amino acid sequences of SEQ ID NO: 189 and 190. Comparison of the isolated sequences with those in the public database revealed no significant homologies to the sequences of SEQ ID NO: 151, 153 and 154. The sequences of SEQ ID NO: 149, 152, 156, 157 and 158 were found to show some homology to previously isolated expressed sequence tags (ESTs). The sequences of SEQ ID NO: 150, 155 and 159-181 were found to show homology to sequences previously identified in humans.

Using the procedures described above, two directional cDNA libraries (referred to as LT46-90 and LT86-21) were prepared from two late passaged lung squamous carcinomas grown in SCID mice and screened with sera obtained from SCID mice implanted with human squamous lung carcinomas. The determined cDNA sequences for the isolated clones are provided in SEQ ID NO: 217-237 and 286-289. SEQ ID NO: 286 was found to be a longer sequence of LT4690-71 (SEQ ID NO: 237). Comparison of these sequences with those in the public databases revealed no known homologies to the sequences of SEQ ID NO: 219, 220, 225, 226, 287 and 288. The sequences of SEQ ID NO: 218, 221, 222 and 224 were found to show some homology to previously identified sequences of unknown function. The sequence of SEQ ID NO: 236 was found to show homology to a known mouse mRNA sequence. The sequences of SEQ ID NO: 217, 223, 227-237, 286 and 289 showed some homology to known human DNA and/or RNA sequences.

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In further studies using the techniques described above, one of the cDNA libraries described above (LT86-21) was screened with *E. coli*-absorbed mouse anti-SCID tumor serum. This serum was obtained from normal mice immunized with a pool of 3 sera taken from SCID mice implanted with human squamous lung carcinomas. The determined cDNA sequences for the isolated clones are provided in SEQ ID NO: 238-285. Comparison of these sequences with those in the public databases revealed no significant homologies to the sequences of SEQ ID NO: 253, 260, 277 and 285. The sequences of SEQ ID NO: 249, 250, 256, 266, 276 and 282 were found to show some homology to previously isolated expressed sequence tags (ESTs). The sequences of SEQ ID NO: 238-248, 251, 252, 254, 255, 257-259, 261-263, 265, 267-275, 278-281, 283 and 284 were found to show some homology to previously identified DNA or RNA sequences.

Full-length sequencing studies on antigen 2LT-128 (SEQ ID NO: 282) resulted in the isolation of the full-length cDNA sequence provided in SEQ ID NO: 392. This amino acid sequence encoded by this full-length cDNA sequence is provided in SEQ ID NO: 393. This antigen shows 20-fold over-expression in squamous cell carcinoma and 2.5-fold over-expression in lung adenocarcinoma. This gene has been described as a potential ras oncogene (Fenwick et al. *Science*, 287:869-873, 2000).

Extended sequence information was obtained for clones 2LT-3 (SEQ ID NO:238), 2LT-26 (SEQ ID NO:242), 2LT-57 (SEQ ID NO: 249), 2LT-58 (SEQ ID NO:250), 2LT-98 (SEQ ID NO:268) and 2LT-124 (SEQ ID NO:279). The extended cDNA sequences for these clones are set forth in SEQ ID NOs:428-433, respectively, encoding the polypeptide sequences set forth in SEQ ID NOs: 434-439, respectively.

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### Example 5

### DETERMINATION OF TISSUE SPECIFICITY OF LUNG TUMOR POLYPEPTIDES

Using gene specific primers, mRNA expression levels for representative lung tumor polypeptides were examined in a variety of normal and tumor tissues using RT-PCR.

Briefly, total RNA was extracted from a variety of normal and tumor tissues using Trizol reagent. First strand synthesis was carried out using 2  $\mu$ g of total RNA with SuperScript II reverse transcriptase (BRL Life Technologies) at 42  $^{0}$ C for one hour. The cDNA was then amplified by PCR with gene-specific primers. To ensure the semi-quantitative nature of the RT-PCR,  $\beta$ -actin was used as an internal control for each of the tissues examined. 1  $\mu$ l of 1:30 dilution of cDNA was employed to enable the linear range amplification of the  $\beta$ -actin template and was sensitive enough to reflect the differences in the initial copy numbers. Using these conditions, the  $\beta$ -actin levels were determined for each reverse transcription reaction from each tissue. DNA contamination was minimized by DNase treatment and by assuring a negative PCR result when using first strand cDNA that was prepared without adding reverse transcriptase.

mRNA Expression levels were examined in five different types of tumor tissue (lung squamous tumor from 3 patients, lung adenocarcinoma, prostate tumor, colon tumor and lung tumor), and different normal tissues, including lung from four patients, prostate, brain, kidney, liver, ovary, skeletal muscle, skin, small intestine, myocardium, retina and testes. L86S-46 was found to be expressed at high levels in lung squamous tumor, colon tumor and prostate tumor, and was undetectable in the other tissues examined. L86S-5 was found to be expressed in the lung tumor samples and in 2 out of 4 normal lung samples, but not in the other normal or tumor tissues tested. L86S-16 was found to be expressed in all tissues except normal liver and normal stomach. Using real-time PCR, L86S-46 was found to be over-expressed in lung squamous tissue and normal tonsil, with expression being low or undetectable in all other tissues examined.

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#### Example 6

### ISOLATION OF DNA SEQUENCES ENCODING LUNG TUMOR ANTIGENS

DNA sequences encoding antigens potentially involved in squamous cell lung tumor formation were isolated as follows.

A lung tumor directional cDNA expression library was constructed employing the Lambda ZAP Express expression system (Stratagene, La Jolla, CA). Total RNA for the library was taken from a pool of two human squamous epithelial lung carcinomas and poly A+ RNA was isolated using oligo-dT cellulose (Gibco BRL, Gaithersburg, MD). Phagemid were rescued at random and the cDNA sequences of isolated clones were determined.

The determined cDNA sequence for the clone SLT-T1 is provided in SEQ ID NO: 102, with the determined 5' cDNA sequences for the clones SLT-T2, SLT-T3, SLT-T5, SLT-T7, SLT-T9, SLT-T10, SLT-T11 and SLT-T12 being provided in SEQ ID NO: 103-110, respectively. The corresponding predicted amino acid sequence for SLT-T1, SLT-T2, SLT-T3, SLT-T10 and SLT-T12 are provided in SEQ ID NO: 111-115, respectively. Comparison of the sequences for SLT-T2, SLT-T3, SLT-T5, SLT-T7, SLT-T9 and SLT-T11 with those in the public databases as described above, revealed no significant homologies. The sequences for SLT-T10 and SLT-T12 were found to show some homology to sequences previously identified in humans.

The sequence of SLT-T1 was determined to show some homology to a PAC clone of unknown protein function. The cDNA sequence of SLT-T1 (SEQ ID NO: 102) was found to contain a mutator (MUTT) domain. Such domains are known to function in removal of damaged guanine from DNA that can cause A to G transversions (see, for example, el-Deiry, W.S., 1997 *Curr. Opin. Oncol.* 9:79-87; Okamoto, K. et al. 1996 *Int. J. Cancer* 65:437-41; Wu, C. et al. 1995 *Biochem. Biophys. Res. Commun.* 214:1239-45; Porter, D.W. et al. 1996 *Chem. Res. Toxicol.* 9:1375-81). SLT-T1 may thus be of use in the treatment, by gene therapy, of lung cancers caused by, or associated with, a disruption in DNA repair.

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In further studies, DNA sequences encoding antigens potentially involved in adenocarcinoma lung tumor formation were isolated as follows. A human lung tumor directional cDNA expression library was constructed employing the Lambda ZAP Express expression system (Stratagene, La Jolla, CA). Total RNA for the library was taken from a late SCID mouse passaged human adenocarcinoma and poly A+ RNA was isolated using the Message Maker kit (Gibco BRL, Gaithersburg, MD). Phagemid were rescued at random and the cDNA sequences of isolated clones were determined.

The determined 5' cDNA sequences for five isolated clones (referred to as SALT-T3, SALT-T4, SALT-T7, SALT-T8, and SALT-T9) are provided in SEQ ID NO: 116-120, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 121-125. SALT-T3 was found to show 98% identity to the previously identified human transducin-like enhancer protein TLE2. SALT-T4 appears to be the human homologue of the mouse H beta 58 gene. SALT-T7 was found to have 97% identity to human 3-mercaptopyruvate sulfurtransferase and SALT-T8 was found to show homology to human interferon-inducible protein 1-8U. SALT-T9 shows approximately 90% identity to human mucin MUC 5B.

cDNA sequences encoding antigens potentially involved in small cell lung carcinoma development were isolated as follows. cDNA expression libraries were constructed with mRNA from the small cell lung carcinoma cell lines NCIH69, NCIH128 and DMS79 (all available from the American Type Culture Collection, Manassas, VA) employing the Lambda ZAP Express expression system (Stratagene, La Jolla, CA). Phagemid were rescued at random and the cDNA sequences of 27 isolated clones were determined. Comparison of the determined cDNA sequences revealed no significant homologies to the sequences of SEQ ID NO: 372 and 373. The sequences of SEQ ID NO: 364, 369, 377, 379 and 386 showed some homology to previously isolated ESTs. The sequences of the remaining 20 clones showed some homology to previously identified genes. The cDNA sequences of these clones are provided in SEQ ID NO: 363, 365-368, 370, 371, 374-376, 378, 380-385 and 387-389, wherein SEQ ID NO: 363, 366-368, 370, 375, 376, 378, 380-382, 384 and 385 are full-length sequences.

Comparison of the cDNA sequence of SEQ ID NO: 372 indicated that this clone (referred to as 128T1) is a novel member of a family of putative seven pass transmembrane proteins. Specifically, using the computer algorithm PSORT, the protein was predicted to be a type IIIA plasma membrane seven pass transmembrane protein. A genomic clone was identified in the Genbank database which contained the predicted N-terminal 58 amino acids missing from the amino acid sequence encoded by SEQ ID NO: 372. The determined full-length cDNA sequence for the 128T1 clone is provided in SEQ ID NO: 390, with the corresponding amino acid sequence being provided in SEQ ID NO: 391.

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#### Example 7

#### SYNTHESIS OF POLYPEPTIDES

Polypeptides may be synthesized on a Perkin Elmer/Applied Biosystems Division 430A peptide synthesizer using FMOC chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

#### Example 8

### ISOLATION AND CHARACTERIZATION OF DNA SEQUENCES ENCODING LUNG TUMOR ANTIGENS BY T-CELL EXPRESSION CLONING

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Lung tumor antigens may also be identified by T cell expression cloning.

One source of tumor specific T cells is from surgically excised tumors from human patients.

A non-small cell lung carcinoma was minced and enzymatically digested for several hours to release tumor cells and infiltrating lymphocytes (tumor infiltrating T cells, or TILs). The cells were washed in HBSS buffer and passed over a Ficoll (100%/75%/HBSS) discontinuous gradient to separate tumor cells and lymphocytes from non-viable cells. Two bands were harvested from the interfaces; the upper band at the 75%/HBSS interface contained predominantly tumor cells, while the lower band at the 100%/75%/HBSS interface contained a majority of lymphocytes. The TILs were expanded in culture, either in 24-well plates with culture media supplemented with 10 ng/ml IL-7 and 100 U/ml IL-2, or alternatively, 24-well plates that have been pre-coated with the anti-CD3 monoclonal antibody OKT3. The resulting TIL cultures were analyzed by FACS to confirm that a high percentage were CD8+ T cells (>90% of gated population) with only a small percentage of CD4+ cells.

In addition, non-small cell lung carcinoma cells were expanded in culture using standard techniques to establish a tumor cell line, which was later confirmed to be a lung carcinoma cell line by immunohistochemical analysis. This tumor cell line was transduced with a retroviral vector to express human CD80, and characterized by FACS analysis to confirm high expression levels of CD80, class I MHC and class II MHC molecules.

The ability of the TIL lines to specifically recognize autologous lung tumor was demonstrated by cytokine release assays (IFN- $\gamma$  and TNF- $\alpha$ ) as well as  $^{51}$ Cr release assays. Briefly, TIL cells from day 21 cultures were co-cultured with either autologous or

allogeneic tumor cells, EBV-immortalized LCL, or control cell lines Daudi and K562, and the culture supernatant monitored by ELISA for the presence of cytokines. The TIL specifically recognized autologous tumor but not allogeneic tumor. In addition, there was no recognition of EBV-immortalized LCL or the control cell lines, indicating that the TIL lines are tumor specific and are potentially recognizing a tumor antigen presented by autologous MHC molecules.

The characterized tumor-specific TIL lines were expanded to suitable numbers for T cell expression cloning using soluble anti-CD3 antibody in culture with irradiated EBV transformed LCLs and PBL feeder cells in the presence of 20 U/ml IL-2. Clones from the expanded TIL lines were generated by standard limiting dilution techniques. Specifically, TIL cells were seeded at 0.5 cells/well in a 96-well U bottom plate and stimulated with CD-80-transduced autologous tumor cells, EBV transformed LCL, and PBL feeder cells in the presence of 50 U/ml IL-2. The specificity of these clones for autologous tumor was confirmed by <sup>51</sup>Cr microcytotoxicity and IFN-γ bioassays.

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These CTL clones were demonstrated to be HLA-B/C restricted by antibody blocking experiments. A representative CTL clone was tested on a panel of allogeneic lung carcinomas and it recognized both autologous tumor and a lung squamous cell carcinoma (936T). As the only class I MHC molecule shared among these tumors was HLA-Cw1203, this indicated that this was the restriction element used by the CTL. This finding was confirmed by the recognition of a number of allogeneic lung carcinomas transduced with a retroviral vector encoding HLA-Cw1203 by the CTL.

PolyA mRNA was prepared from lung tumor LT391-06 cells using Message Maker (Life Technologies; Rockville, MD). The subsequent steps involving cDNA synthesis were performed according to Life Technologies cloning manual (SuperScript Plasmid System for cDNA Synthesis and Plasmid Cloning). Modifications to the protocol were made as follows. At the adapter addition step, EcoRI-XmnI adapters (d(AATTCGAACCCCTTCG), New England Biolabs; Beverly, MA) were substituted. Size fractionated cDNAs were ligated into the expression vector system HisMax A, B, C

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(Invitrogen; Carlsbad, CA) to optimize for protein expression in all three coding frames. Library plasmids were then aliquotted at approximately 100 CFU/well into a 96-well block for overnight liquid amplification. From these cultures, glycerols stocks were made and pooled plasmid was prepared by auotmated robot (Qiagen; Valencia, CA). The concentration of the plasmid DNA in each well of the library plates was determined to be approximately 150 ng/ul. For T cell screening, approximately 80 ng of the library plasmid DNA and 80 ng of HLA-Cw1203 plasmid DNA was mixed with the lipid Fugene according the the manufacturers instructions and transfected in duplicate into COS-7 cells. After incubation at 37 C for 48 hours, the transfection mixture was removed and 10,000 LT391-06 CTL were added to each well in fresh media containing human serum.

The ability of the T cells to recognize an antigen in the library was assessed by cytokine release after 6 hours (TNF-alpha, WEHI bio-assay) or after 24 hours (IFN-gamma, ELISA). Approximately ~2.0 x 10<sup>5</sup> clones (in plasmid pools of 100) have been screened using this system in COS-7 cells. Three plasmid pools were identified (14F10, 19A4, and 20E10) that were recognized by LT391-06 CTL. Transfection of these plasmid pools into COS-7 cells led to production of both IFN-gamma and TNF-alpha from the LT391-06 CTL significantly above background. Pools 14F10 and 19A4 were "broken down" into several hundred individual plasmid DNAs and retested. One plasmid (3D9) from pool 14F10 and 5 plasmids (2A6, 2E11, 2F12, 3F4, 3H8) from 19A4 pool were capable of reconstituting T cell recognition.

The sequencing of these plasmids identified a 7.8 kB cDNA insert (clone 14F10) and also a 2.2 kB cDNA insert (clone 19A4; SEQ ID NO:440). Clone 19A4 is contained within the 5' region of clone 14F10. BLAST search analysis against the GenBank database identified both of these sequences as having significant homology with a truncated human cystine/glutamate transporter gene. Unlike the published sequence, however, clones 14F10 and 19A4 contained a unique 5' terminus consisting of 181 nucleotides. This novel sequence replaces the published 5' region and results in the removal of the reported initiating methionine (start codon) and an additional two amino acids of the reported transporter protein. Therefore, the translated product of clones 14F10 and 19A4 is

different than the cystine/glutamate transporter protein. Furthermore, T cell recognition of other lung tumors demonstrates that this antigen is expressed by other tumors as well.

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

#### **CLAIMS**

#### What is claimed:

- 1. An isolated polypeptide, comprising at least an immunogenic portion of a lung tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (a) sequences recited in SEQ ID NOs: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359, 361, 364, 369, 372, 373, 377, 379, 386, 390, 392 and 440;
- (b) sequences that hybridize to a sequence recited in any one of SEQ ID NOs: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359, 361, 364, 369, 372, 373, 377, 379, 386, 390, 392 and 440 under moderately stringent conditions; and
  - (c) complements of sequences of (a) or (b).
- 2. An isolated polypeptide according to claim 1, wherein the polypeptide comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359, 361, 364, 369, 372, 373, 377, 379, 386, 390, 392 and 440 or a complement of any of the foregoing polynucleotide sequences.
- 3. An isolated polypeptide comprising a sequence recited in any one of SEQ ID NO: 391, 393, 395, 397, 421 and 425-427.
- 4. An isolated polynucleotide encoding at least 15 amino acid residues of a lung tumor protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the tumor protein comprises an amino acid

sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NOs: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359, 361, 364, 369, 372, 373, 377, 379, 386, 390, 392 and 440, or a complement of any of the foregoing sequences.

- 5. An isolated polynucleotide encoding a lung tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NOs: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359, 361, 364, 369, 372, 373, 377, 379, 386, 390, 392 and 440 or a complement of any of the foregoing sequences.
- 6. An isolated polynucleotide, comprising a sequence recited in any one of SEQ ID NOs: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359, 361, 364, 369, 372, 373, 377, 379, 386, 390, 392 and 440.
- 7. An isolated polynucleotide, comprising a sequence that hybridizes to a sequence recited in any one of SEQ ID NOs: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359, 361, 364, 369, 372, 373, 377, 379, 386, 390, 392 and 440 under moderately stringent conditions.
- 8. An isolated polynucleotide complementary to a polynucleotide according to any one of claims 4-7.
- 9. An expression vector, comprising a polynucleotide according to any one of claims 4-8.

- 10. A host cell transformed or transfected with an expression vector according to claim 9.
- 11. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a lung tumor protein that comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359, 361, 364, 369, 372, 373, 377, 379, 386, 390, 392 and 440 or a complement of any of the foregoing polynucleotide sequences.
  - 12. A fusion protein, comprising at least one polypeptide according to claim 1.
- 13. A fusion protein according to claim 12, wherein the fusion protein comprises an expression enhancer that increases expression of the fusion protein in a host cell transfected with a polynucleotide encoding the fusion protein.
- 14. A fusion protein according to claim 12, wherein the fusion protein comprises a T helper epitope that is not present within the polypeptide of claim 1.
- 15. A fusion protein according to claim 12, wherein the fusion protein comprises an affinity tag.
- 16. An isolated polynucleotide encoding a fusion protein according to claim 12.
- 17. A pharmaceutical composition, comprising a physiologically acceptable carrier and at least one component selected from the group consisting of:
  - (a) a polypeptide according to claim 1;
  - (b) a polynucleotide according to claim 4;

- (c) an antibody according to claim 11;
- (d) a fusion protein according to claim 12; and
- (e) a polynucleotide according to claim 16.
- 18. An immunogenic composition comprising an immunostimulant and at least one component selected from the group consisting of:
  - (a) a polypeptide according to claim 1;
  - (b) a polynucleotide according to claim 4;
  - (c) an antibody according to claim 11;
  - (d) a fusion protein according to claim 12; and
  - (e) a polynucleotide according to claim 16.
- 19. An immunogenic composition according to claim 18, wherein the immunostimulant is an adjuvant.
- 20. An immunogenic composition according to claim 18, wherein the immunostimulant induces a predominantly Type I response.
- 21. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a pharmaceutical composition according to claim 17.
- 22. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an immunogenic composition according to claim 18.
- 23. A pharmaceutical composition comprising an antigen-presenting cell that expresses a polypeptide according to claim 1, in combination with a pharmaceutically acceptable carrier or excipient.

- 24. A pharmaceutical composition according to claim 23, wherein the antigen presenting cell is a dendritic cell or a macrophage.
- 25. An immunogenic composition comprising an antigen-presenting cell that expresses a polypeptide comprising at least an immunogenic portion of a lung tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (a) sequences recited in SEQ ID NOs: 217-390, 392, 394, 396, 398-420, 422-424, 428-433 and 440;
- (b) sequences that hybridize to a sequence recited in any one of SEQ ID NOs: 217-390, 392, 394, 396, 398-420, 422-424, 428-433 and 440 under moderately stringent conditions; and
  - (c) complements of sequences of (i) or (ii); in combination with an immunostimulant.
- 26. An immunogenic composition according to claim 25, wherein the immunostimulant is an adjuvant.
- 27. An immunogenic composition according to claim 25, wherein the immunostimulant induces a predominantly Type I response.
- 28. An immunogenic composition according to claim 25, wherein the antigenpresenting cell is a dendritic cell.
- 29. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an antigen-presenting cell that expresses a polypeptide comprising at least an immunogenic portion of a lung tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

- (a) sequences recited in SEQ ID NOs: 217-390, 392, 394, 396, 398-420, 422-424, 428-433 and 440;
- (b) sequences that hybridize to a sequence recited in any one of SEQ ID NOs: 217-390, 392, 394, 396, 398-420, 422-424, 428-433 and 440 under moderately stringent conditions; and
  - (c) complements of sequences of (i) or (ii); and thereby inhibiting the development of a cancer in the patient.
- 30. A method according to claim 29, wherein the antigen-presenting cell is a dendritic cell.
- 31. A method according to any one of claims 21, 22 and 29, wherein the cancer is lung cancer.
- 32. A method for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a lung tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (i) polynucleotides recited in any one of SEQ ID NOs: 217-390, 392, 394, 396, 398-420, 422-424, 428-433 and 440; and
  - (ii) complements of the foregoing polynucleotides;

wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the antigen from the sample.

33. A method according to claim 32, wherein the biological sample is blood or a fraction thereof.

- 34. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated according to the method of claim 32.
- 35. A method for stimulating and/or expanding T cells specific for a lung tumor protein, comprising contacting T cells with at least one component selected from the group consisting of:
- (a) polypeptides comprising at least an immunogenic portion of a lung tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (i) sequences recited in SEQ ID NOs: 217-390, 392, 396, 398-420, 422-424, 428-433 and 440;
- (ii) sequences that hybridize to a sequence recited in any one of SEQ ID NOs: 217-390, 392, 396, 398-420, 422-424, 428-433 and 440 under moderately stringent conditions; and
  - (iii) complements of sequences of (i) or (ii);
  - (b) polynucleotides encoding a polypeptide of (a); and
  - (c) antigen presenting cells that express a polypeptide of (a);

under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

- 36. An isolated T cell population, comprising T cells prepared according to the method of claim 35.
- 37. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient with a binding agent that binds to a lung tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs: 217-

390, 392, 394, 396, 398-420, 422-424, 428-433 and 440 or a complement of any of the foregoing polynucleotide sequences;

- (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and
- (c) comparing the amount of polypeptide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.
  - 38. A method according to claim 37, wherein the binding agent is an antibody.
- 39. A method according to claim 38, wherein the antibody is a monoclonal antibody.

# COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF LUNG CANCER

#### ABSTRACT OF THE DISCLOSURE

Compositions and methods for the therapy and diagnosis of cancer, such as lung cancer, are disclosed. Compositions may comprise one or more lung tumor proteins, immunogenic portions thereof, or polynucleotides that encode such portions. Alternatively, a therapeutic composition may comprise an antigen presenting cell that expresses a lung tumor protein, or a T cell that is specific for cells expressing such a protein. Such compositions may be used, for example, for the prevention and treatment of diseases such as lung cancer. Diagnostic methods based on detecting a lung tumor protein, or mRNA encoding such a protein, in a sample are also provided.

#### IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Steven G. Reed et al. Filed : September 20, 2000

For : COMPOSITIONS AND METHODS FOR THE THERAPY AND

DIAGNOSIS OF LUNG CANCER

Docket No. : 210121.475C7

Date : September 20, 2000

Box Patent Application Assistant Commissioner for Patents Washington, D.C. 20231

#### **DECLARATION**

Sir:

I, Monica Steinborn, in accordance with 37 C.F.R. § 1.821(f) do hereby declare that, to the best of my knowledge, the content of the paper entitled "Sequence Listing" and the computer readable copy contained within the floppy disk are the same.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated this 20<sup>th</sup> day of September, 2000.

Monica Steinborn

Biotechnology Paralegal

701 Fifth Avenue, Suite 6300 Seattle, WA 98104-7092 (206) 622-4900 FAX (206) 682-6031 Wpn/210121 - Corixa/475c7/Seq/475c7.dec doc

#### SEQUENCE LISTING

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tgaaatattt cagacctacg ngagggctta aagacnaatt aaatgagcac cngtgtgccc
accgccccna ttaagaatta gagcaagcag tgaggtgaag ccttgtcctt gcttttaaca
                                                                        180
tagaaagtga tccaaattca ccaaacttga cttnnggttt tgcagtgtgg cctcctgatt
                                                                        240
ctagacnctg gcgaaacatt tgatgggcaa aaaaaaaaaa
                                                                        280
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      <211> 449
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
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      <223> n = A, T, C or G
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ntgcagtgct natgactggc tttgcagttn attttgattc aggcaacaga tgttcctttt
                                                                        120
ggttccctgt ctcccatggg cgtcatttca tgttgtcctc tgccttcccc cagatattct
                                                                        180
aagttcagga cacaagcttc tggcccatgc agagcagagg ccatgagggg tcacagcatg
                                                                        240
ggtacgggag gaaacactgg gctnacccag atnctggact tgagtcttgc ctctgctgct
                                                                        300
tgctgcacag cttctgtcat ggtgctaaac ctgtgacctg cctcacaggc ttagagcatg
                                                                        360
cccgtagaag tactctnaac taaratgett tecacaaatg agatggttte atgaaaactt
                                                                        420
                                                                        449
caaatagagg qcctgggcaa aaaaaaaaa
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      <211> 538
      <212> DNA
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      <221> misc feature
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      <223> n = A, T, C or G
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atcogcoggg atacatgcca cttggtttga taaatcaaaa tacagcatcc ttcagatccc
                                                                        120
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tttgctgagc aatacaatta tttgtatatg ttactttttt ttctgtttgg ctnaaagatt
                                                                        180
tgatatgage tgaggaaaat gaageentta etgetatnag atetnateee tttecaceae
                                                                        240
                                                                        300
ctttcaqqqa tnttqqcact qcayatattc aqaattcccc nnagtcqctn gtgataaaaa
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tgtcttcaga gatggcagaa tatgtttcct ttggtacatg ttcattaaaa atatacacgt
                                                                        420
qctcactact qtqqatatqt atqtnttqac cqatnacaca qqctqattta qqqaaqaqat
                                                                        480
aaaagcacac ttngaattta ttagcctttc accnagacta anattctgaa attaagaatg
                                                                        538
tatteettgg teaacaattt teetettete ttageeetet tacattgtan tggaetga
      <210> 11
      <211> 543
      <212> DNA
      <213> Homo sapien
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      <221> misc feature
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      <223> n = A, T, C or G
      <400> 11
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caaccetcqc catcccaqca aatcccctct ctcccttctc atgggagtgc cttgtattca
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tcaggcatct gggacttgat gtgggtntgg gatttgaaat cagagcacct nggtctctst
                                                                        180
caccattetn teaettatta getetnaeet tgggtnaata cetgeettag tgtentaggt
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acaatatgaa tattgtctat ttctcaggga ttgcaatgac nagtnnatna gtgcatgaga
                                                                        300
                                                                        360
qqqtaaaacc acaqqqtact ccqctcctcc naaqaatqqa qaattttttc taqaaqccca
natntgcttg gaaggttggc caccnagagc cnnaatcttc ttttatttnc cactgaangc
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ctaagaggna attctgaact catccccnna tgacctctcc cgaatmagaa tatctctggc
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acttaccata ttttcttgcc ctcttccact tacnaaactc ctttattcct taacnggacg
                                                                        540
                                                                        543
aaa
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      <211> 329
      <212> DNA
      <213> Homo sapien
      <400> 12
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ccttggcctc cccctctgc agstacctct gaccaagaag gaaactagca agcctatgct
                                                                        120
                                                                       180
ggcaagacca taggtggggt gctgggaatc ctcggggccg gctggcaccc actcctggtg
                                                                        240
ctcaaqqqaq aqaccactt qttcaqatqc atrqqcctca qqcqqttcaa qqcrqtctta
                                                                       300
gagccacaga qtcaaataaa aatcaatttt qagaqaccac agcacctgct gctttgatcg
                                                                        329
tgatgttcaa ggcaagttgc aagtcatcg
      <210> 13
      <211> 314
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(314)
      <223> n = A, T, C or G
      <400> 13
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60
cqatqacttq cacccqqqaq ctqtqacaqt ggcctggaaq cagatggcag ccccgtcaag
                                                                       120
qeqqqaqtqq aqaccaccaa accetecaaa caqaqcaaca actagtacge ggecagcage
                                                                       180
tacctgagcc tgacgcccga gcagtggaag tcccacagaa gctacagctg ccaggtcacg
                                                                       240
catgaaggga gcaccgtgga gaagacagtg gcccctacag aatgttcata ggttcccnac
                                                                       300
tctnaccca cccacgggag cctgganctg cangatcccg ggggaagggt ctctctcccc
                                                                       314
atcccaagtc atcg
      <210> 14
      <211> 691
      <212> DNA
      <213> Homo sapien
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      <221> misc feature
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      <223> n = A, T, C or G
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qaaqaqaaqa ataaaqtcta ttttqqtctt tqqtaqcchq qqtaanqaqa atgctstcac
                                                                       180
tctacnaqaa aacccnaaqt gaacccggct aatcaggacc gtgcttggga agggagcagg
                                                                       240
ggcattacct ttcaacacca gaggttcttt gccttctctc tgcagggact cgargactat
                                                                       300
                                                                       360
qtqaaqtqqc tqqqarqqca tcactcqqct tggttcattq gtrttctcat cataaactat
natttetttg qaaaaagate etettgaaag arteettgee tteeetacag gaaatcaagt
                                                                       420
ctaggacagt gatcttqccc ctqcttgcas tctccgccgg ctgatcttat csgscccagt
                                                                       480
tkatgtqsam cqctccttqq atrtkactct tqttttwctc cvaggaaggg gcytgcmagt
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ccnwtnaatg amssqggccc ttaactccgg scrggtnamy ncttgsctsc rattttgggt
                                                                       600
yeytetteyt ttgsccmqqt tektenaaac caettngttr aatteecegg seegeetkge
                                                                       660
nggtycaacc wttttgggaa mamcyccccc c
                                                                       691
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      <211> 355
      <212> DNA
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      <221> misc feature
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acceptgecta tgtccgacag ctagttnect ccatggatgt gactgagace aatgtettet
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                                                                       180
toyaccetcg getettacet ttgacnaagt etceegttga gagtactace gaaccaccag
                                                                       240
cagttcgagc ctctnaagag cgtctaagcg atggggatat atatttactg gagaatgggc
                                                                       300
tcaacctctt cctctqqqtq qqaqcaaqcq tccaqcaqqq tqttqtccaq aqccttttca
qcqtctcctc cttcaqtcaq atcaccaqtq qtntqaqtqt tctqccaqtt caggt
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      <210> 16
      <211> 522
      <212> DNA
      <213> Homo sapien
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<220>
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      <222> (1)...(522)
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                                                                     120
                                                                     180
tttcttgaac aaaagttctg aagatgatgc ggcctcagag agcttcctcc cctcggaagg
                                                                     240
tgcgtcctct gaccccgtga ccctncgtcg aangatgctg gctgccgccg cggaacggan
                                                                     300
getteagaag cageagaeet cetngegete cettgeette eteagetgee teetgegeee
tgtgcccggc tgactggagg aggcctgtcc aattctgccc gccccatgga aaagcgggct
                                                                     360
tgactgcatt gccgctgtat naaagcatgt ggtcttacag tgttnggacn gctnatnaat
                                                                     420
                                                                     480
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                                                                     522
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aaggataagc accagagaaa gaaggttcag ccggccgtcc tgaaatatta taaggtggat
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gagaatggca aaattagttg cettegtega gagtgeeeet etgatgaatg tggtgetggg
gtgtttatgg caagtcactt tgacagacat tattgtggca aatgttgtct gacccactgt
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                                                                     300
ttcaactaac cagaagacaa gtaactgtat gagttaatta aagacatgaa ctaaaaaaaa
                                                                     317
aaaaaaaaa actcgag
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      <211> 392
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agaageeect gaeeeettat tteegettet teatggagaa gegggeeaag tatgegaaae
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                                                                     240
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360
gagegaaacc tggcccgatt cagggaggat cacccccacc ttatccagaa tgccaagaat
                                                                     392
cggacatccc agagaagccc caagaccccc cg
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                                                                     120
tcttgggctg cccactgccg gatcctaata actattatca ccgacgtaat gagatgacca
                                                                     180
ccacggatga cctggatttt aagcaccaca actattagga aatgcgccag ttgatgaagg
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360
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                                                                      1740
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aatccatcct ctctggcccc aggggacaag ccaagctgct atgtacacac tcggtgttct
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                                                                      2280
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cagtcagggc atcttggaaa agaccttgaa ggaagcaaac cctgggttcc ttttgctcca
                                                                      2340
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gccacatctt gccaatcaag catcatctga tgaaaaagaa agcaatctta ggattacctg
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ggacacgtca gtctgggaga ggtggttgaa tcattgtgta agggaatagt gtatctaatc
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tgtgttgatc ctgctgcctt gttgacctgg agagaatgaa acaaacaaac acataaacaa
                                                                      2624
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                                                                       120
                                                                       180
gctggacagc tggaggatga acggagaagc cgactgcccc acagacctgg aaatggccgc
                                                                       240
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```

ggaaaaagtt gcattgaaag acttttctgg agacatgtgc aagctcaaat gggtcgagat

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tgtttaaaat ccttacaaag gcaaaaaatc aagaaacacc ccgacttccc cgagaaagcc

360

420

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	gagcgagact ttgtctcaaa	aaagaagaaa	agatattatt	cccatcatga	tttcttgtga	1200
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	ccacaggctt tggggtggct	ctcctactgg	ctctttttgg	cegigeetee	gaggacccgc	240

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actqtqcatt qcacactqtt accatqqqtt tatqctcact atcatatcac attqccaata
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acagaacatg taataatgaa gtggtcaaaa tgcagaggct aacattagaa cacttgaatc
                                                                       180
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ggaagcaaca geggeagtee cetgeecaag ttateceaet agetgattae tatateattg
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ctggagtgat ctatcaggca ccagacttgg gatcagttat aaactctaga gtgcttactg
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cagtgcatgg tattcagtca gcttttgatg aagctatgtc atactgtcga tatcatcctt
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ccaaagggta ttggtggcac ttcaaagatc atgaagagca agataaagtc agacctaaag

600

660

720

780

840 900

960

1020 1080

1140

1200

1260

1320 1355

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ccaaaaggaa agaagaacca agetetattt tteagagaca aegtgtggat getttaettt
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Thr Thr Pro Lys Lys Asp Lys His Gln Arg Lys Lys Val Gln Pro Ala
                                25
Val Leu Lys Tyr Tyr Lys Val Asp Glu Asn Gly Lys Ile Ser Cys Leu
                            40
Arg Arg Glu Cys Pro Ser Asp Glu Cys Gly Ala Gly Val Phe Met Ala
                        55
Ser His Phe Asp Arg His Tyr Cys Gly Lys Cys Cys Leu Thr His Cys
                                        75
      <210> 33
      <211> 130
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      <213> Homo sapien
      <400> 33
Glu Ile Ser Asn Glu Val Arg Lys Phe Arg Thr Leu Thr Glu Leu Ile
Leu Asp Ala Gln Glu His Val Lys Asn Pro Tyr Lys Gly Lys Lys Leu
            20
                                25
Lys Lys His Pro Asp Phe Pro Lys Lys Pro Leu Thr Pro Tyr Phe Arg
                            40
Phe Phe Met Glu Lys Arg Ala Lys Tyr Ala Lys Leu His Pro Gln Met
                        55
                                            60
Ser Asn Leu Asp Leu Thr Lys Ile Leu Ser Lys Lys Tyr Lys Glu Leu
                    70
                                        75
Pro Glu Lys Lys Met Lys Tyr Val Pro Asp Phe Gln Arg Arg Glu
                85
                                    90
Thr Gly Val Arg Ala Lys Pro Gly Pro Ile Gln Gly Gly Ser Pro Pro
            100
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Pro Tyr Pro Glu Cys Gln Glu Ser Asp Ile Pro Glu Lys Pro Gln Asp

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120
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Pro Pro
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Val Ala Arg Tyr Ile Arg Ile Asn Pro Gln Ser Trp Phe Asp Asn Gly
          20
                            25
Ser Ile Cys Met Arg Met Glu Ile Leu Gly Cys Pro Leu Pro Asp Pro
Asn Asn Tyr Tyr His Arg Arg Asn Glu Met Thr Thr Asp Asp Leu
                    55
Asp Phe Lys His His Asn Tyr Lys Glu Met Arg Gln Leu Met Lys Val
Val Asn Glu Met Cys Pro Asn Ile Thr Arg Ile Tyr Asn Ile Gly Lys
        85
                               90
Ser His Gln Gly Leu Lys Leu Tyr Ala Val Glu Ile Ser Asp His Pro
                           105
         100
Gly Glu His Glu Val Gly Glu Pro Glu Phe His Tyr Ile Ala Gly Ala
                                         125
                        120
His Gly Asn Glu Val Leu Gly Arg Glu Leu Leu Leu Leu Leu His
                     135
                                      140
Phe Leu Cys Gln Glu Tyr Ser Ala Gln Asn Ala Arg Ile Val Arg Leu
                 150
                                   155
Val Glu Glu Thr Arg Ile His Ile Leu Pro Ser Leu Asn Pro Asp Gly
                               170
             165
                                                 175
Tyr Glu Lys Ala Tyr Glu Gly Gly Ser Glu Leu Gly Gly Trp Ser Leu
                           185
Gly Arg Trp Thr His Asp Gly Ile Asp Ile Asn Asn Asn Phe Pro Asp
                        200
                                         205
      195
Leu Asn Ser Leu Leu Trp Glu Ala Glu Asp Gln Gln Asn Ala Pro Arg
                    215
                            220
Lys Val Pro Asn His Tyr Ile Ala Ile Pro Glu Trp Phe Leu Ser Glu
                     235 240
     230
Asn Ala Thr Val Ala Thr Glu Thr Arg Ala Val Ile Ala Trp Met Glu
                               250
              245
Lys Ile Pro Phe Val Leu Gly Gly Asn Leu Gln Gly Gly Glu Leu Val
                            265
Val Ala Tyr Pro Tyr Asp Met Val Arg Ser Leu Trp Lys Thr Gln Glu
                        280
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His Thr Pro Thr Pro Asp Asp His Val Phe Arg Trp Leu Ala Tyr Ser
                   295
                                      300
Tyr Ala Ser Thr His Arg Leu Met Thr Asp Ala Arg Arg Val Cys
                                  315
                 310
His Thr Glu Asp Phe Gln Lys Glu Glu Gly Thr Val Asn Gly Ala Ser
             325 330
Trp His Thr Val Ala Gly Ser Leu Asn Asp Phe Ser Tyr Leu His Thr
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          340
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Asn Cys Phe Glu Leu Ser Ile Tyr Val Gly Cys Asp Lys Tyr Pro His
                            360
Glu Ser Glu Leu Pro Glu Glu Trp Glu Asn Asn Arg Glu Ser Leu Ile
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                       375
Val Phe Met Glu Gln Val His Arg Gly Ile Lys Gly Ile Val Arg Asp
                                       395
                   390
Leu Gln Gly Lys Gly Ile Ser Asn Ala Val Ile Ser Val Glu Gly Val
                                410
               405
Asn His Asp Ile Arg Thr Ala Ser Asp Gly Asp Tyr Trp Arg Leu Leu
                              425
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Asn Pro Gly Glu Tyr Val Val Thr Ala Lys Ala Glu Gly Phe Ile Thr
        435
                           440
                                    445
Ser Thr Lys Asn Cys Met Val Gly Tyr Asp Met Gly Ala Thr Arg Cys
                                           460
                        455
Asp Phe Thr Leu Thr Lys Thr Asn Leu Ala Arg Ile Arg Glu Ile Met
                                       475
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Glu Thr Phe Gly Lys Gln Pro Val Ser Leu Pro Ser Arg Arg Leu Lys
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Leu Arg Gly Arg Lys Arg Arg Gln Arg Gly
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Met Asn Gly Glu Ala Asp Cys Pro Thr Asp Leu Glu Met Ala Ala Pro
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Arg Gly Gln Asp Arg Trp Ser Gln Glu Asp Met Leu Thr Leu Leu Glu
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Cys Met Lys Asn Asn Leu Pro Ser Asn Asp Ser Ser Gln Phe Lys Thr
                            40
Thr Gln Thr His Met Asp Arg Glu Lys Val Ala Leu Lys Asp Phe Ser
                       55
Gly Asp Met Cys Lys Leu Lys Trp Val Glu Ile Ser Asn Glu Val Arg
                                       75
                    70
Lys Phe Arg Thr Leu Thr Glu Leu Ile Leu Asp Thr Gln Glu His Val
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      <210> 36
      <211> 129
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      <213> Homo sapien
      <400> 36
Gly Ile Val Val Phe Ser Leu Gly Ser Met Val Ser Glu Ile Pro Glu
                                   10
Lys Lys Ala Val Ala Ile Ala Asp Ala Leu Gly Lys Ile Pro Gln Thr
                                25
           20
Val Leu Trp Arg Tyr Thr Gly Thr Arg Pro Ser Asn Leu Ala Asn Asn
                            40
Thr Ile Leu Val Gln Trp Leu Pro Gln Asn Asp Leu Leu Gly His Pro
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      Met
      Thr
      Arg
      Ala
      Phe
      Ile
      Thr
      His
      Ala
      Ser
      Ser
      His
      Gly
      Val
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      Ile
      Ser
      His
      Gly
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      A
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<210> 37 <211> 238

<212> PRT

<213> Homo sapien

<400> 37

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235

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<211> 202

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<400> 38

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                          40
Ser Arg Gln Gly Ser Ser Leu Asn Leu Phe Glu Asp Val Gln Ile Thr
                     55
Glu Pro Glu Ala Glu Pro Glu Ser Lys Ser Glu Pro Arg Pro Pro Ile
                                      75
                  70
Ser Ser Pro Arg Ala Pro Gln Thr Arg Ala Val Lys Pro Arg Leu His
                                  90
Pro Val Lys Pro Met Asn Ala Thr Ala Thr Lys Val Ala Asn Cys Ser
                              105
Leu Gly Thr Ala Thr Ile Ile Gly Glu Asn Leu Asn Asn Glu Val Met
                          120
Met Lys Lys Tyr Ser Pro Ser Asp Pro Ala Phe Ala Tyr Ala Gln Leu
                      135
Thr His Asp Glu Leu Ile Gln Leu Val Leu Lys Gln Lys Glu Thr Ile
                  150
                                     155
Ser Lys Lys Glu Phe Gln Val Arg Glu Leu Glu Asp Tyr Ile Asp Asn
                              170
              165
Leu Leu Val Arg Val Met Glu Glu Thr Pro Asn Ile Leu Arg Ile Pro
                             185
          180
Thr Gln Val Gly Lys Lys Ala Gly Lys Met
     <210> 39
     <211> 243
      <212> PRT
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     <400> 39
Val Asn Ala Leu Gly Ile Met Ala Ala Val Asp Ile Arg Asp Asn Leu
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Leu Gly Ile Ser Trp Val Asp Ser Ser Trp Ile Pro Ile Leu Asn Ser
                               25
          20
Gly Ser Val Leu Asp Tyr Phe Ser Glu Arg Ser Asn Pro Phe Tyr Asp
                                              45
                          40
Arg Thr Cys Asn Asn Glu Val Val Lys Met Gln Arg Leu Thr Leu Glu
                       55
His Leu Asn Gln Met Val Gly Ile Glu Tyr Ile Leu Leu His Ala Gln
                                      75
Glu Pro Ile Leu Phe Ile Ile Arg Lys Gln Gln Arg Gln Ser Pro Ala
Gln Val Ile Pro Leu Ala Asp Tyr Tyr Ile Ile Ala Gly Val Ile Tyr
                              105
Gln Ala Pro Asp Leu Gly Ser Val Ile Asn Ser Arg Val Leu Thr Ala
                          120
Val His Gly Ile Gln Ser Ala Phe Asp Glu Ala Met Ser Tyr Cys Arg
                       135
                                          140
Tyr His Pro Ser Lys Gly Tyr Trp Trp His Phe Lys Asp His Glu Glu
145 150 155
Gln Asp Lys Val Arg Pro Lys Ala Lys Arg Lys Glu Glu Pro Ser Ser
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<210> 40 <211> 245 <212> PRT <213> Homo sapien

<400> 40

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<210> 41

<211> 163 <212> PRT

## <213> Homo sapien

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<210> 42

<211> 243

<212> PRT

<213> Homo sapien

<400> 42

Val Asp Ile Arg Asp Asn Leu Leu Gly Ile Ser Trp Val Asp Ser Ser 10 Trp Ile Pro Ile Leu Asn Ser Gly Ser Val Leu Asp Tyr Phe Ser Glu 20 25 Arg Ser Asn Pro Phe Tyr Asp Arg Thr Cys Asn Asn Glu Val Val Lys 40 Met Gln Arg Leu Thr Leu Glu His Leu Asn Gln Met Val Gly Ile Glu 55 Tyr Ile Leu Leu His Ala Gln Glu Pro Ile Leu Phe Ile Ile Arg Lys 70 75 Gln Gln Arg Gln Ser Pro Ala Gln Val Ile Pro Leu Ala Asp Tyr Tyr Ile Ile Ala Gly Val Ile Tyr Gln Ala Pro Asp Leu Gly Ser Val Ile 100 105 Asn Ser Arg Val Leu Thr Ala Val His Gly Ile Gln Ser Ala Phe Asp 120 Glu Ala Met Ser Tyr Cys Arg Tyr His Pro Ser Lys Gly Tyr Trp Trp 140 135 His Phe Lys Asp His Glu Glu Gln Asp Lys Val Arg Pro Lys Ala Lys 150 155 Arg Lys Glu Glu Pro Ser Ser Ile Phe Gln Arg Gln Arg Val Asp Ala 165 170

arg hea Gin

<210> 43

<211> 244

<212> PRT

<213> Homo sapien

<400> 43

Ala Val Asp Ile Arg Asp Asn Leu Leu Gly Ile Ser Trp Val Asp Ser Ser Trp Ile Pro Ile Leu Asn Ser Gly Ser Val Leu Asp Tyr Phe Ser 20 25 Glu Arg Ser Asn Pro Phe Tyr Asp Arg Thr Cys Asn Asn Glu Val Val 40 Lys Met Gln Arg Leu Thr Leu Glu His Leu Asn Gln Met Val Gly Ile 55 60 Glu Tyr Ile Leu Leu His Ala Gln Glu Pro Ile Leu Phe Ile Ile Arg 70 75 Lys Gln Gln Arg Gln Ser Pro Ala Gln Val Ile Pro Leu Ala Asp Tyr 85 90 Tyr Ile Ile Ala Gly Val Ile Tyr Gln Ala Pro Asp Leu Gly Ser Val 100 105 Ile Asn Ser Arg Val Leu Thr Ala Val His Gly Ile Gln Ser Ala Phe 120 Asp Glu Ala Met Ser Tyr Cys Arg Tyr His Pro Ser Lys Gly Tyr Trp 140 135 Trp His Phe Lys Asp His Glu Glu Gln Asp Lys Val Arg Pro Lys Ala 150 155 Lys Arg Lys Glu Glu Pro Ser Ser Ile Phe Gln Arg Gln Arg Val Asp 170 165 Ala Leu Leu Leu Asp Leu Arg Gln Lys Phe Pro Pro Lys Phe Val Gln 180 185 Leu Lys Pro Gly Glu Lys Pro Val Pro Val Asp Gln Thr Lys Lys Glu 200 Ala Glu Pro Ile Pro Glu Thr Val Lys Pro Glu Glu Lys Glu Thr Thr 215 220 Lys Asn Val Gln Gln Thr Val Ser Ala Lys Gly Pro Pro Glu Lys Arg 230 235 Met Arg Leu Gln

<210> 44

<211> 109

<212> PRT

<213> Homo sapien

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Ser Val Ala Asp Arg Asp Asn Ser Pro Ser Ser Cys Ala Gly Leu Phe
                               25
Ile Ala Ser His Ile Gly Phe Asp Trp Pro Gly Val Trp Val His Leu
                           40
Asp Ile Ala Ala Pro Val His Ala Gly Glu Arg Ala Thr Gly Phe Gly
                       55
Val Ala Leu Leu Ala Leu Phe Gly Arg Ala Ser Glu Asp Pro Leu
                                      75
Leu Asn Leu Val Ser Pro Leu Asp Cys Glu Val Asp Ala Gln Glu Gly
                                  90
Asp Asn Met Gly Arg Asp Ser Lys Arg Arg Leu Val
     <210> 45
      <211> 324
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Ser Arg Gly Asp Ser Pro Ile Ile Glu Lys Met Glu Lys Arg Thr Cys
                               25
           20
Ala Leu Cys Pro Glu Gly His Glu Trp Ser Gln Ile Tyr Phe Ser Pro
                           40
Ser Gly Asn Ile Val Ala His Glu Asn Cys Leu Leu Tyr Ser Ser Gly
                       55
Leu Val Glu Cys Glu Thr Leu Asp Leu Arg Asn Thr Ile Arg Asn Phe
                                       75
Asp Val Lys Ser Val Lys Lys Glu Ile Trp Arg Gly Arg Arg Leu Lys
                                   90
               85
Cys Ser Phe Cys Asn Lys Gly Gly Ala Thr Val Gly Cys Asp Leu Trp
                               105
Phe Cys Lys Lys Ser Tyr His Tyr Val Cys Ala Lys Lys Asp Gln Ala
                           120
Ile Leu Gln Val Asp Gly Asn His Gly Thr Tyr Lys Leu Phe Cys Pro
                       135
                                          140
Glu His Ser Pro Glu Gln Glu Glu Ala Thr Glu Ser Ala Asp Asp Pro
                   150
                                       155
Ser Met Lys Lys Arg Gly Lys Asn Lys Arg Leu Ser Ser Gly Pro
               165
                                   170
                                                       175
Pro Ala Gln Pro Lys Thr Met Lys Cys Ser Asn Ala Lys Arg His Met
                              185
Thr Glu Glu Pro His Gly His Thr Asp Ala Ala Val Lys Ser Pro Phe
                           200
Leu Lys Lys Cys Gln Glu Ala Gly Leu Leu Thr Glu Leu Phe Glu His
                      215
                                          220
Ile Leu Glu Asn Met Asp Ser Val His Gly Arg Leu Val Asp Glu Thr
                  230
                                      235
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Ala Ser Glu Ser Asp Tyr Glu Gly Ile Glu Thr Leu Leu Phe Asp Cys

Gly Leu Phe Lys Asp Thr Leu Arg Lys Phe Gln Glu Val Ile Lys Ser 265

Lys Ala Cys Glu Trp Glu Glu Arg Gln Arg Gln Met Lys Gln Glu Leu 270

Glu Ala Leu Ala Asp Leu Gln Gln Ser Leu Cys Ser Phe Gln Glu Asp 290

Gly Asp Leu Asp Cys Ser Ser Ser Thr Ser Gly Ser Leu Leu Pro Pro 305

Glu Asp His Gln

<210> 46 <211> 244 <212> PRT <213> Homo sapien

<400> 46

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Thr Met Tyr Arg 1 Arg Ala Pro Ala 20	g Ala Leu Arg Leu 5 a Ala Ala Leu Ala c Phe Trp Pro Pro 40	10 Ser Ala Pro 25	Gly Leu Gly	15 / Gly Ala	

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Asn Asp Lys Tyr Tyr Gly Ala Gln Thr Val Arg Ser Thr Met Asn Phe
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                   70
Lys Ile Gly Gly Val Thr Glu Arg Met Pro Thr Pro Val Ile Lys Ala
                                  90
Phe Gly Ile Leu Lys Arg Ala Ala Ala Glu Val Asn Gln Asp Tyr Gly
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           100
Leu Asp Pro Lys Ile Ala Asn Ala Ile Met Lys Ala Ala Asp Glu Val
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Ala Glu Gly Lys Leu Asn Asp His Phe Pro Leu Val Val Trp Gln Thr
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Gly Ser Gly Thr Gln Thr Asn Met Asn Val Asn Glu Val Ile Ser
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Gln Lys Gln Pro Phe Ser Ile Glu Glu Ile Glu Val Ala Pro Pro Lys
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Thr Lys Glu Val Arg Ile Lys Ile Leu Ala Thr Gly Ile Cys Arg Thr
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Asp Asp His Val Ile Lys Gly Thr Met Val Ser Lys Phe Pro Val Ile
                   70
                                       75
Val Gly His Glu Ala Thr Gly Ile Val Glu Ser Ile Gly Glu Gly Val
                                   90
Thr Thr Val Lys Pro Gly Asp Lys Val Ile Pro Leu Phe Leu Pro Gln
                               105
           100
Cys Arg Glu Cys Asn Ala Cys Arg Asn Pro Asp Gly Asn Leu Cys Ile
                           120
Arg Ser Asp Ile Thr Gly Arg Gly Val Leu Ala Asp Gly Thr Thr Arg
                       135
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Phe Thr Cys Lys Gly Glu Pro Val His His Phe Met Asn Thr Ser Thr
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Phe Thr Glu Tyr Thr
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Tyr Lys Ala Thr Val Ala Ser Asp Gln Ile Glu Met Asn Arg Leu Lys
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Ala Gln Leu Glu Asn Glu Lys Gln Lys Val Ala Glu Leu Tyr Ser Ile
His Asn Ser Gly Asp Lys Ser Asp Ile Gln Asp Leu Leu Glu Ser Val
Arg Leu Asp Lys Glu Lys Ala Glu Thr Leu Ala Ser Ser Leu Gln Glu
                                       75
                   70
Asp Leu Ala His Thr Arg Asn Asp Ala Asn Arg Leu Gln Asp Ala Ile
               85
                                   90
Ala Lys Val Glu Asp Glu Tyr Arg Ala Phe Gln Glu Glu Ala Lys Lys
           100
                              105
Gln Ile Glu Asp Leu Asn Met Thr Leu Glu Lys Leu Arg Ser Asp Leu
                           120
Asp Glu Lys Glu Thr Glu Arg Ser Asp Met Lys Glu Thr Ile Phe Glu
                       135
                                            140
Leu Glu Asp Glu Val Glu Gln His Arg Ala Val Lys Leu His Asp Asn
                   150
                                        155
Leu Ile Ile Ser Asp Leu Glu Asn Thr Val Lys Lys Leu Gln Asp Gln
                                   170
               165
Lys His Asp Met Glu Arg Glu Ile Lys Thr Leu His Arg Arg Leu Arg
                            185
           180
Glu Glu Ser Ala Glu Trp Arg Gln Phe Gln Ala Asp Leu Gln Thr Ala
                           200
      195
Val Val Ile Ala Asn Asp Ile Lys Ser Glu Ala Gln Glu Glu Ile Gly
                                            220
                       215
Asp Leu Lys Arg Arg Leu His Glu Ala Gln Glu Lys Asn Glu Lys Leu
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                                       235
Thr Lys Glu Leu Glu Glu Ile Lys Ser Arg Lys Gln Glu Glu Glu Arg
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Gly Gly Tyr
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            20
                                25
Pro Gln Asp Leu Pro Tyr Pro Asp Pro Ala Ile Ala Gln Phe Ser Val
                            40
Gln Lys Val Thr Pro Gln Ser Asp Gly Ser Ser Ser Lys Val Lys Val
                        55
Lys Val Arg Val Asn Val His Gly Ile Phe Ser Val Ser Ser Ala Ser
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Leu Val Glu Val His Lys Ser Glu Glu Asn Glu Glu Pro Met Glu Thr

Asp Gln Asn Ala Lys Glu Glu Glu Lys Met Gln Val Asp Gln Glu Glu
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120

Pro His Val Glu Glu Gln Gln Gln Thr Pro Gly Arg

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90

70

8.5

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245

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Phe Tyr Arg Ser Ser Phe Gln Leu Leu Asn Val Glu Tyr Asn Ser Gln
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Leu Asn Ser Pro Ala Thr Gln Glu Tyr Arg Thr Leu Ser Gly Arg Ile
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                  70
Glu Ser Leu Ile Thr Lys Thr Phe Lys Glu Ser Asn Leu Arg Asn Gln
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              85
Phe Ile Arg Ala His Val Ala Lys Leu Arg Gln Asp Gly Ser Gly Val
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Arg Ala Asp Val Val Met Lys Phe Gln Phe Thr Arg Asn Asn Asn Gly
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                          120
Ala Ser Met Lys Ser Arg Ile Glu Ser Val Leu Arg Gln Met Leu Asn
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                                        140
Asn Ser Gly Asn Leu Glu Ile Asn Pro Ser Thr Glu Ile Thr Ser Leu
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                                     155
Thr Asp Gln Ala Ala Asn Trp Leu Ile Asn Glu Cys Gly Ala Gly
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Pro Asp Leu Ile Thr Leu Ser Glu Gln Arg Ile Leu Gly Gly Thr Glu
          180
                             185
Ala Glu Glu Gly Ser Trp Pro Trp Gln Val Ser Leu Arg Leu Asn Asn
                                205
                         200
Ala His His Cys Gly Gly Ser Leu Ile Asn Asn Met Trp Ile Leu Thr
                      215
Ala Ala His Cys Phe Arg Ser Asn Ser Asn Pro Arg Asp Trp Ile Ala
                   230
                                      235
Thr Ser Gly Ile Ser Thr Thr Phe Pro Lys Leu Arg Met Arg Val Arg
                                 250
              245
Asn Ile Leu Ile His Asn Asn Tyr Lys Ser Ala Thr His Glu Asn Asp
          260 265
Ile Ala Leu Val Arg Leu Glu Asn Ser Val Thr Phe Thr Lys Asp Ile
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His Ser Val Cys Leu Pro Ala Ala Thr Gln Asn Ile Pro Pro Gly Ser
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                                         300
Thr Ala Tyr Val Thr Gly Trp Gly Ala Gln Glu Tyr Ala Gly His Thr
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Val Pro Glu Leu Arg Gln Gly Gln Val Arg Ile Ile Ser Asn Asp Val
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Cys Asn Ala Pro His Ser Tyr Asn Gly Ala Ile Leu Ser Gly Met Leu
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            340
Cys Ala Gly Val Pro Gln Gly Gly Val Asp Ala Cys Gln Gly Asp Ser
                                                365
                            360
Gly Gly Pro Leu Val Gln Glu Asp Ser Arg Arg Leu Trp Phe Ile Val
                        375
                                            380
    370
Gly Ile Val Ser Trp Gly Asp Gln Cys Gly Leu Pro Asp Lys Pro Gly
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Val Tyr Thr Arg Val Thr Ala Tyr Ile Asp Trp Ile Arg Gln Gln Thr
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tatgatgttg gagcacacgc agaaggtcca aaatgattgg cttcatgaag gatttaagaa
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actotyttgc ccaggotyga gtacagtygt gcaatotoag otoactgcaa cototycoto
ctgggttcaa gagattcacc tgcctcagcc ccctagtagc tgggattata ggtgtacacc
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Ala Ala Lys Met Met Ser Ala Ala Ala Ile Ala Asn Gly Gly Val

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Ala Ser Gly Ser Leu Val Ala Thr Leu Gln Ser Leu Gly Ala Thr Gly 35 40 45

Leu Ser Gly Leu Thr Lys Phe Ile Leu Gly Ser Ile Gly Ser Ala Ile 50 55 60

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<213> Homo sapien

<400> 67

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			• • •					245					250		
7. ~~	П.т.	C1.,	340 Val	Cl.,	Tou	LOU	7.20	345	T 🔿 1 1	Clu	Ser	T.011	350 Pro	Glu	Glu
_	_	355					360					365			
	370		Arg			375					380				
Lys 385	Gln	Ala	Thr	Ser	Pro 390	Ala	Ser	Lys	Lys	Pro 395	Ala	Gln	Glu	Gly	Gly 400
	Gly	Gly	Ser	Glu 405		Pro	Lys	Arg	Pro 410	Val	Ser	Ala	Met	Phe 415	Ile
Phe	Ser	Glu	Glu 420		Arg	Arg	Gln	Leu 425		Glu	Glu	Arg	Pro 430	Glu	Leu
Ser	Glu	Ser 435	Glu	Leu	Thr	Arg	Leu 440		Ala	Arg	Met	Trp	Asn	Asp	Leu
Ser	Glu 450		Lys	Lys	Ala	Lys 455		Lys	Ala	Arg	Glu 460	Ala	Ala	Leu	Lys
Ala 465		Ser	Glu	Arg	Lys 470		Gly	Gly	Glu	Arg 475		Glu	Arg	Gly	Lys 480
	Pro	Glu	Ser	Pro 485		Arg	Ala	Glu	Glu 490		Trp	Gln	Gln	Ser 495	
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Lys	Ala	Met 515		Met	Thr	Trp	Asn 520		Met	Glu	Lys	Lys 525		Lys	Leu
Met	Trp 530		Lys	Lys	Ala	Ala 535		Asp	Gln	Lys	Arg 540		Glu	Arg	Glu
Leu 545		Glu	Met	Arg	Ala 550		Pro	Ala	Ala	Thr 555	Asn	Ser	Ser	Lys	Lys 560
	Lys	Phe	Gln	Gly 565		Pro	Lys	Lys	Pro 570	Pro	Met	Asn	Gly	Tyr 575	Gln
Lys	Phe	Ser	Gln 580		Leu	Leu	Ser	Asn 585	Gly	Glu	Leu	Asn	His 590	Leu	Pro
Leu	Lys	Glu 595	Arg	Met	Val	Glu	Ile 600	Gly	Ser	Arg	Trp	Gln 605	Arg	Ile	Ser
Gln	Ser 610	Gln	Lys	Glu	His	Tyr 615	Lys	Lys	Leu	Ala	Glu 620	Glu	Gln	Gln	Lys
Gln 625	Tyr	Lys	Val	His	Leu 630	Asp	Leu	Trp	Val	Lys 635	Ser	Leu	Ser	Pro	Gln 640
Asp	Arg	Ala	Ala	615	Lys				Ser 650		Lys		Lys	Ser 655	Met
Thr	Lys	Leu	Arg 660	Gly	Pro	Asn	Pro	Lys 665		Ser	Arg	Thr	Thr 670	Leu	Gln
Ser	Lys	Ser 675	Glu	Ser	Glu	Glu	Asp 680	Asp	Glu	Glu	Asp	Glu 685	Asp	Asp	Glu
Asp	Glu 690	Asp	Glu	Glu	Glu	Glu 695	Asp	Asp	Glu	Asn	Gly 700	Asp	Ser	Ser	Glu
Asp 705	Gly	Gly	Asp	Ser	Ser 710	Glu	Ser	Ser	Ser	Glu 715	Asp	Glu	Ser	Glu	Asp 720
	Asp	Glu	Asn	Glu 725		Asp	Asp	Glu	Asp 730	Glu	Asp	Asp	Asp	Glu 735	Asp
Asp	Asp	Glu	Asp 740		Asp	Asn	Glu	Ser 745		Gly	Ser	Ser	Ser 750	Ser	Ser
Ser	Ser	Leu 755	Gly	Asp	Ser	Ser	Asp 760	Phe	Asp	Ser	Asn				

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<210> 69 <211> 244 <212> DNA <213> Homo sapien	
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<210> 70 <211> 437 <212> DNA <213> Homo sapien	
<400> 70 ctgggacggg agcgtccagc gggactcgaa ccccagatgt gaaggcgttt ctggaaagtccttggtccet ggatccagcg tcggccagcc cagagccgt gccgcacatc cttgcgtcctccaggcagtg ggaccccgcg agctgcacgt ccctgggcac ggacaagtgt gaggcactgt tggggctgtg ccaggtgcgg ggtgggctgc cccctttctc agaaccttcc agcctggtgccgtgtgcccccaggcacctgtcctgt	120 180 240 300 360
<210> 71 <211> 271 <212> DNA <213> Homo sapien	
<400> 71 gcgcagagtt ctgtcgtcca ccatcgagtg aggaagagag cattggttcc cctgagatagagagagagagagagagagagagagagagag	g 120 a 180

180

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<210> 72
      <211> 290
      <212> DNA
      <213> Homo sapien
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ctggtgccct ctcctgctgc gaggactcgg cccagggctc gggcccgccc aaggccccta
cqqtqqccqa qqqtcccagc tcctgccttc ggcggaacgt gatcagcgag agggagcgca
ggaagcggat gtcgttgagc tgtgagcgtc tgcgggccct gctgccccag ttcgatggcc
ggcgggagga catggcctcg gtcctggaga tgtctgttgc aattcctgcg
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Lys Ala Ile Met Thr Tyr Val Ser Ser Phe Tyr His Ala Phe Ser Gly
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            20
Ala Gln Lys Ala Glu Thr Ala Ala Asn Arg Ile Cys Lys Val Leu Ala
                                                 45
                            40
Val Asn Gln Glu Asn Glu Gln Leu Met Glu Asp Tyr Glu Lys Leu Ala
                                             60
                        55
Ser Asp Leu Leu Glu Trp Ile Arg Arg Thr Ile Pro Trp Leu Glu Asn
                                        75
                    70
Arg Val Pro Glu Asn Thr Met His Ala Met Gln Gln Lys Leu Glu Asp
Phe Arg Asp Tyr Arg Arg Leu His Lys Pro Pro Lys Val Gln Glu Lys
                                105
            100
Cys Gln Leu Glu Ile Asn Phe Asn Thr Leu Gln Thr Lys Leu Arg Leu
                            120
                                                125
Ser Asn Arg Pro Ala Phe Met Pro Ser Glu Gly Arg Met Val Ser Asp
                                             140
                        135
    130
      <210> 74
      <211> 64
      <212> PRT
      <213> Homo sapien
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Gly Ser Met Leu Val Glu Ser His His His Ser Leu Ile Ser Ser Thr
Gln Gly His Lys His Cys Gly Arg Pro Gln Gly Pro Leu Pro Arg Lys
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Thr Arg Asp Leu Cys Ser Leu Val Tyr Val Leu Thr Phe Pro Pro Leu
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Leu Ser Cys Asp Pro Ala Lys Ser Pro Phe Val Arg Asn Thr Gln Glu
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<212> PRT

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<213> Homo sapien
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Leu Glu Ser Pro Trp Ser Leu Asp Pro Ala Ser Ala Ser Pro Glu Pro
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       20
Val Pro His Ile Leu Ala Ser Ser Arg Gln Trp Asp Pro Ala Ser Cys
                           40
Thr Ser Leu Gly Thr Asp Lys Cys Glu Ala Leu Leu Gly Leu Cys Gln
                     55
Val Arg Gly Gly Leu Pro Pro Phe Ser Glu Pro Ser Ser Leu Val Pro
                                      75
                   70
Trp Pro Pro Gly Arg Ser Leu Pro Lys Ala Val Arg Pro Pro Leu Ser
                                   90
Trp Pro Pro Phe Ser Gln Gln Gln Thr Leu Pro Val Met Ser Gly Glu
                               105
Ala Leu Gly Trp Leu Gly Gln Ala Gly Ser Leu Ala Met Gly Ala Ala
                          120
Pro Leu Gly Glu Pro Ala Lys Glu Asp Pro Met Leu Ala Gln Glu Ala
                       135
Gly
145
      <210> 76
      <211> 69
     <212> PRT
      <213> Homo sapien
      <400> 76
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Pro Glu Ile Glu Glu Met Ala Leu Phe Ser Ala Gln Ser Pro Tyr Ile
Asn Pro Ile Ile Pro Phe Thr Gly Pro Ile Gln Gly Gly Leu Gln Glu
                           40
Gly Leu Gln Val Thr Leu Gln Gly Thr Thr Glu Ser Phe Ala Gln Lys
Phe Val Val Asn Phe
65
      <210> 77
      <211> 96
      <212> PRT
      <213> Homo sapien
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Glu Pro Tyr Pro Glu Val Ser Arg Ile Pro Thr Val Arg Gly Cys Asn
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Gly Ser Leu Ser Gly Ala Leu Ser Cys Cys Glu Asp Ser Ala Gln Gly
                               25
Ser Gly Pro Pro Lys Ala Pro Thr Val Ala Glu Gly Pro Ser Ser Cys
                            40
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Leu Arg Arg Asn Val Ile Ser Glu Arg Glu Arg Arg Lys Arg Met Ser Leu Ser Cys Glu Arg Leu Arg Ala Leu Leu Pro Gln Phe Asp Gly Arg 75 70 Arg Glu Asp Met Ala Ser Val Leu Glu Met Ser Val Ala Ile Pro Ala 90 <210> 78 <211> 2076 <212> DNA <213> Homo sapien <400> 78 60 agaaaaagtc tatgtttgca gaaatacaga tccaagacaa agacaggatg ggcactgctg gaaaagttat taaatgcaaa gcagctgtgc tttgggagca gaagcaaccc ttctccattg 120 aggaaataga agttgcccca ccaaagacta aagaagttcg cattaagatt ttggccacag 180 gaatctgtcg cacagatgac catgtgataa aaggaacaat ggtgtccaag tttccagtga 240 ttgtgggaca tgaggcaact gggattgtag agagcattgg agaaggagtg actacagtga 300 360 aaccaggtga caaagtcatc cctctcttc tgccacaatg tagagaatgc aatgcttgtc 420 gcaacccaga tggcaacctt tgcattagga gcgatattac tggtcgtgga gtactggctg 480 atggcaccac cagatttaca tgcaagggca aaccagtcca ccacttcatg aacaccagta 540 catttaccga gtacacagtg gtggatgaat cttctgttgc taagattgat gatgcagctc 600 ctcctgagaa agtctgttta attggctgtg ggttttccac tggatatggc gctgctgtta 660 aaactggcaa ggtcaaacct ggttccactt gcgtcgtctt tggcctgaga ggagttggcc 720 tgtcagtcat catgggctgt aagtcagctg gtgcatctag gatcattggg attgacctca 780 acaaagacaa atttgagaag gccatggctg taggtgccac tgagtgtatc agtcccaagg 840 actctaccaa acccatcagt gaggtgctgt cagaaatgac aggcaacaac gtgggataca 900 cctttgaagt tattgggcat cttgaaacca tgattgatgc cctggcatcc tgccacatga actatgggac cagcgtggtt gtaggagttc ctccatcagc caagatgctc acctatgacc 960 cgatgttgct cttcactgga cgcacatgga agggatgtgt ctttggaggt ttgaaaagca 1020 1080 gagatgatgt cccaaaacta gtgactgagt tcctggcaaa gaaatttgac ctggaccagt tgataactca tgtcttacca tttaaaaaaa tcagtgaagg atttgagctg ctcaattcag 1140 gacaaagcat tcgaacggtc ctgacgtttt gagatccaaa gtggcaggag gtctgtgttg 1200 tcatggtgaa ctggagtttc tcttgtgaga gttccctcat ctgaaatcat gtatctgtct 1260 cacaaataca agcataagta gaagatttgt tgaagacata gaacccttat aaagaattat 1320 taacctttat aaacatttaa agtcttgtga gcacctggga attagtataa taacaatgtt 1380 1440 aatatttttg atttacattt tgtaaggcta taattgtatc ttttaagaaa acatacactt ggatttctat gttgaaatgg agatttttaa gagttttaac cagctgctgc agatatatat 1500 1560 ctcaaaacag atatagcgta taaagatata gtaaatgcat ctcctagagt aatattcact taacacattg aaactattat tttttagatt tgaatataaa tgtattttt aaacacttgt 1620 1680 tatgagttaa cttggattac attttgaaat cagttcattc catgatgcat attactggat 1740 tagattaaga aagacagaaa agattaaggg acgggcacat ttttcaacga ttaagaatca 1800 tcattacata acttqqtqaa actqaaaaaq tatatcatat gggtacacaa ggctatttgc 1860 cagcatatat taatatttta gaaaatattc cttttgtaat actgaatata aacatagagc 1920 tagaatcata ttatcatact tatcataatg ttcaatttga tacagtagaa ttgcaagtcc ttaagtccct attcactgtg cttagtagtg actccattta ataaaaagtg tttttagttt 1980 ttaacaacta cactgatgta tttatatata tttataacat gttaaaaaatt tttaaggaaa 2040

2076

ttaaaaatta tataaaaaaa aaaaaaaaaa ctcgag

<sup>&</sup>lt;210> 79 <211> 2790

<sup>&</sup>lt;212> DNA

<sup>&</sup>lt;213> Homo sapien

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<sup>&</sup>lt;210> 80

<sup>&</sup>lt;211> 1460

<sup>&</sup>lt;212> DNA

<sup>&</sup>lt;213> Homo sapien

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gtcgcagggg tagtgatcct ggcagtcacc atagctctac ttgtttactt tttagctttt
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gatcaaaaat cttactttta taggagcagt tttcaactcc taaatgttga atataatagt
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cagttaaatt caccagctac acaggaatac aggactttga gtggaagaat tgaatctctg
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                                                                       360
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                                                                       420
agaaataaca atggagcatc aatgaaaagc agaattgagt ctgttttacg acaaatgctg
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                                                                       540
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gctgcagcaa attggcttat taatgaatgt ggggccggtc cagacctaat aacattgtct
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                                                                       660
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                                                                       840
atttccacaa catttcctaa actaagaatg agagtaagaa atattttaat.tcataacaat
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tataaatctg caactcatga aaatgacatt gcacttgtga gacttgagaa cagtgtcacc
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tctactgctt atgtaacagg atggggggct caagaatatg ctggccacac agttccagag
                                                                      1020
                                                                      1080
ctaaggcaag gacaggtcag aataataagt aatgatgtat gtaatgcacc acatagttat
                                                                      1140
aatggagcca tcttgtctgg aatgctgtgt gctggagtac ctcaaggtgg agtggacgca
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tgtcagggtg actctggtgg cccactagta caagaagact cacggcggct ttggtttatt
                                                                      1260
gtggggatag taagctgggg agatcagtgt ggcctgccgg ataagccagg agtgtatact
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cgagtgacag cctaccttga ctggattagg caacaaactg ggatctagtg caacaagtgc
                                                                      1380
atccctqttq caaaqtctqt atqcaqqtqt gcctqtctta aattccaaaq ctttacattt
caactgaaaa agaaactaga aatgtcctaa tttaacatct tgttacataa atatggttta
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                                                                      1460
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<210> 81 <211> 386 <212> PRT <213> Homo sapien

<400> 81

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170
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Pro Pro Glu Lys Val Cys Leu Ile Gly Cys Gly Phe Ser Thr Gly Tyr
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Gly Ala Ala Val Lys Thr Gly Lys Val Lys Pro Gly Ser Thr Cys Val
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Val Phe Gly Leu Arg Gly Val Gly Leu Ser Val Ile Met Gly Cys Lys
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Ser Ala Gly Ala Ser Arg Ile Ile Gly Ile Asp Leu Asn Lys Asp Lys
                   230
                                      235
Phe Glu Lys Ala Met Ala Val Gly Ala Thr Glu Cys Ile Ser Pro Lys
                                 250
              245
Asp Ser Thr Lys Pro Ile Ser Glu Val Leu Ser Glu Met Thr Gly Asn
                              265
           260
Asn Val Gly Tyr Thr Phe Glu Val Ile Gly His Leu Glu Thr Met Ile
                           280
Asp Ala Leu Ala Ser Cys His Met Asn Tyr Gly Thr Ser Val Val Val
                       295
Gly Val Pro Pro Ser Ala Lys Met Leu Thr Tyr Asp Pro Met Leu Leu
                                      315
                  310
Phe Thr Gly Arg Thr Trp Lys Gly Cys Val Phe Gly Gly Leu Lys Ser
                                  330
               325
Arg Asp Asp Val Pro Lys Leu Val Thr Glu Phe Leu Ala Lys Lys Phe
          340
                              345
Asp Leu Asp Gln Leu Ile Thr His Val Leu Pro Phe Lys Lys Ile Ser
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Glu Gly Phe Glu Leu Leu Asn Ser Gly Gln Ser Ile Arg Thr Val Leu
Thr Phe
385
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     <211> 418
      <212> PRT
     <213> Homo sapien
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           20
Thr Ile Ala Leu Leu Val Tyr Phe Leu Ala Phe Asp Gln Lys Ser Tyr
                           40
Phe Tyr Arg Ser Ser Phe Gln Leu Leu Asn Val Glu Tyr Asn Ser Gln
                       55
Leu Asn Ser Pro Ala Thr Gln Glu Tyr Arg Thr Leu Ser Gly Arg Ile
                                       75
                   70
Glu Ser Leu Ile Thr Lys Thr Phe Lys Glu Ser Asn Leu Arg Asn Gln
                                  90
Phe Ile Arg Ala His Val Ala Lys Leu Arg Gln Asp Gly Ser Gly Val
           100
                              105
Arg Ala Asp Val Val Met Lys Phe Gln Phe Thr Arg Asn Asn Asn Gly
                          120
                                              125
Ala Ser Met Lys Ser Arg Ile Glu Ser Val Leu Arg Gln Met Leu Asn
                       135
    130
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Asn Ser Gly Asn Leu Glu Ile Asn Pro Ser Thr Glu Ile Thr Ser Leu
                                     155
                  150
Thr Asp Gln Ala Ala Ala Asn Trp Leu Ile Asn Glu Cys Gly Ala Gly
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              165
Pro Asp Leu Ile Thr Leu Ser Glu Gln Arg Ile Leu Gly Gly Thr Glu
                             185
          180
Ala Glu Glu Gly Ser Trp Pro Trp Gln Val Ser Leu Arg Leu Asn Asn
               200
Ala His His Cys Gly Gly Ser Leu Ile Asn Asn Met Trp Ile Leu Thr
        215
                              220
Ala Ala His Cys Phe Arg Ser Asn Ser Asn Pro Arg Asp Trp Ile Ala
                       235
                 230
Thr Ser Gly Ile Ser Thr Thr Phe Pro Lys Leu Arg Met Arg Val Arg
                                 250
               245
Asn Ile Leu Ile His Asn Asn Tyr Lys Ser Ala Thr His Glu Asn Asp
                              265
Ile Ala Leu Val Arg Leu Glu Asn Ser Val Thr Phe Thr Lys Asp Ile
                         280
His Ser Val Cys Leu Pro Ala Ala Thr Gln Asn Ile Pro Pro Gly Ser
                                        300
                      295
Thr Ala Tyr Val Thr Gly Trp Gly Ala Gln Glu Tyr Ala Gly His Thr
                  310
                                     315
Val Pro Glu Leu Arg Gln Gly Gln Val Arg Ile Ile Ser Asn Asp Val
                                 330
              325
Cys Asn Ala Pro His Ser Tyr Asn Gly Ala Ile Leu Ser Gly Met Leu
                             345
Cys Ala Gly Val Pro Gln Gly Gly Val Asp Ala Cys Gln Gly Asp Ser
                          360
       355
Gly Gly Pro Leu Val Gln Glu Asp Ser Arg Arg Leu Trp Phe Ile Val
                      375
                                         380
Gly Ile Val Ser Trp Gly Asp Gln Cys Gly Leu Pro Asp Lys Pro Gly
                  390
                                     395
Val Tyr Thr Arg Val Thr Ala Tyr Leu Asp Trp Ile Arg Gln Gln Thr
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                                 410
Gly Ile
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<210> 83

<211> 418

<212> PRT

<213> Homo sapien

<400> 83

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 Tyr
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 Pro
 Ala
 Arg
 Val
 Thr
 Ser
 Thr
 Ser
 Arg
 Phe
 Leu
 Asn
 Pro

 Tyr
 Val
 Val
 Val
 Val
 Val
 Val
 Ile
 Leu
 Ala
 Val

 Thr
 Ile
 Ala
 Leu
 Val
 Tyr
 Phe
 Leu
 Ala
 Phe
 Leu
 Ala
 Phe
 Ala
 Phe
 Ala
 Phe
 Ala
 Phe
 Ala
 Phe
 Ala
 Ala
 Ala
 Phe
 Ala
 Ala
 Phe
 Ala
 Ala

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90
Phe Ile Arg Ala His Val Ala Lys Leu Arg Gln Asp Gly Ser Gly Val
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           100
Arg Ala Asp Val Val Met Lys Phe Gln Phe Thr Arg Asn Asn Asn Gly
                                               125
                           120
       115
Ala Ser Met Lys Ser Arg Ile Glu Ser Val Leu Arg Gln Met Leu Asn
                       135
Asn Ser Gly Asn Leu Glu Ile Asn Pro Ser Thr Glu Ile Thr Ser Leu
                                       155
                   150
Thr Asp Gln Ala Ala Ala Asn Trp Leu Ile Asn Glu Cys Gly Ala Gly
                                   170
               165
Pro Asp Leu Ile Thr Leu Ser Glu Gln Arg Ile Leu Gly Gly Thr Glu
                              185
Ala Glu Glu Gly Ser Trp Pro Trp Gln Val Ser Leu Arg Leu Asn Asn
                                               205
                           200
        195
Ala His His Cys Gly Gly Ser Leu Ile Asn Asn Met Trp Ile Leu Thr
                                           220
                       215
Ala Ala His Cys Phe Arg Ser Asn Ser Asn Pro Arg Asp Trp Ile Ala
                                      235
                   230
Thr Ser Gly Ile Ser Thr Thr Phe Pro Lys Leu Arg Met Arg Val Arg
                                   250
               245
Asn Ile Leu Ile His Asn Asn Tyr Lys Ser Ala Thr His Glu Asn Asp
                                                   270
                              265
           260
Ile Ala Leu Val Arg Leu Glu Asn Ser Val Thr Phe Thr Lys Asp Ile
                           280
                                               285
        275
His Ser Val Cys Leu Pro Ala Ala Thr Gln Asn Ile Pro Pro Gly Ser
                       295
                                           300
Thr Ala Tyr Val Thr Gly Trp Gly Ala Gln Glu Tyr Ala Gly His Thr
                                       315
                   310
Val Pro Glu Leu Arg Gln Gly Gln Val Arg Ile Ile Ser Asn Asp Val
                325
                                   330
                                                       335
Cys Asn Ala Pro His Ser Tyr Asn Gly Ala Ile Leu Ser Gly Met Leu
            340
                               345
Cys Ala Gly Val Pro Gln Gly Gly Val Asp Ala Cys Gln Gly Asp Ser
                           360
Gly Gly Pro Leu Val Gln Glu Asp Ser Arg Arg Leu Trp Phe Ile Val
                       375
                                           380
Gly Ile Val Ser Trp Gly Asp Gln Cys Gly Leu Pro Asp Lys Pro Gly
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                                       395
Val Tyr Thr Arg Val Thr Ala Tyr Leu Asp Trp Ile Arg Gln Gln Thr
               405
                                   410
Gly Ile
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<210> 84

<211> 489

<212> DNA

<213> Homo sapien

### <400> 84

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agctacagta tgttttggac gtttgaatgg agtgccaata agctagtaga ccctgaacgg ccattcacct gtgggacctg aagttctaa	ttgtccgaag gacatgagct	aggagttgtc tgaggttgaa	attgttggat tgaacagtat	gaattctata gaacatgcct	300 360 420 480 489
<210> 85 <211> 304 <212> DNA <213> Homo sapie	en				
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<210> 86 <211> 296 <212> DNA <213> Homo sapio	en				
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<210> 87 <211> 904 <212> DNA <213> Homo sapid	en				
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<210> 89 <211> 481 <212> DNA <213> Homo sapi	en				
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actacatggt ttacatgttc caatatgatt ccacccatgg caaattccat ggcaccgtcg
                                                                       240
                                                                       300
aggctgagaa cgggaagctt gtcatcaatg gaaatcccat caccatcttc caggagcgag
                                                                       360
atcoctccaa aatcaagtgg ggcgatgctg gcgctgagta cgtcgtggag tccactggcg
                                                                       420
tetteaceae catggagaag getggggete atttgcaggg gggagecaaa agggteatea
                                                                       480
tetetgeece tetgetgatg ecceatgtte gteatgggtg tgaaccatga gaagtatgae
                                                                       488
acaqcctc
      <210> 92
      <211> 384
      <212> DNA
      <213> Homo sapien
      <400> 92
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                                                                        60
qqaaqqtqaa qqtcqqaqtc aacqqatttq qtcqtattqq gcgcctggtc accaqggctq
                                                                       120
cttttaactc tggtaaagtg gatattgttg ccatcaatga ccccttcatt gacctcaact
                                                                       180
acatggttta catgttccaa tatgattcca cccatggcaa attccatggc accgtcgagg
                                                                       240
                                                                       300
ctgagaacgg gaagcttgtc atcaatggaa atcccatcac catcttccag gagcgagatc
                                                                       360
cctccaaaat caagtggggc gatactggcg ctgagtacgt cgtggagtcc actggcgtct
                                                                       384
tcaccaccat ggagaaggct gggg
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      <211> 162
      <212> PRT
      <213> Homo sapien
      <400> 93
Lys Gly Lys Leu Asp Asp Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg
Leu Asn Gln Asp Gln Leu Asp Ala Val Ser Lys Tyr Gln Glu Val Thr
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                                25
Asn Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg Ser Phe Met Ala Leu
                            40
Ser Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln
                        55
Leu Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu
                                         75
Leu Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp Glu Val Arg Thr Asp
                85
                                    90
Leu Lys Gln Gly Leu Asn Gly Val Pro Ile Leu Ser Glu Glu Glu Leu
Ser Leu Leu Asp Glu Phe Tyr Lys Leu Val Asp Pro Glu Arg Asp Met
        115
                                                 125
                            120
Ser Leu Arg Leu Asn Glu Gln Tyr Glu His Ala Ser Ile His Leu Trp
                        135
                                             140
Asp Leu Leu Glu Gly Lys Glu Lys Pro Val Cys Gly Thr Thr Tyr Lys
145
                    150
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Val Leu
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<210> 94

<211> 100

<212> PRT

#### <213> Homo sapien

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Lys Ile Leu Pro Leu Asn Gly Asn Leu Gln Ala Val Glu Leu Gly Glu 10 Lys Arg Thr Ser Ser Leu Arg Ile Lys Met Phe Arg Ala Thr Arg Val 25 Thr Ser Thr Ser Arg Phe Leu Asn Pro Tyr Val Val Cys Phe Leu Val 40 Leu Pro Gly Val Val Ile Leu Ala Val Pro Ile Ala Leu Leu Val Tyr 55 Phe Leu Ala Phe Asp Gln Lys Ser Tyr Phe Tyr Trp Ser Asn Phe Pro 70 75 Leu Pro Asn Val Glu Tyr Asn Ser Pro Phe Asn Ser Pro Ala Ser Pro Gly Ile Pro

<210> 96 <211> 257 <212> PRT <213> Homo sapien

<400> 96

Val Gln Glu Thr Ile His Glu His Asn Lys Leu Ala Ala Asn Ser Asp 10 His Leu Met Gln Ile Gln Lys Cys Glu Leu Val Leu Ile His Thr Tyr 25 Pro Val Gly Glu Asp Ser Leu Val Ser Asp Arg Ser Lys Lys Glu Leu 40 Ser Pro Val Leu Thr Ser Glu Val His Ser Val Arg Ala Gly Arg His 55 Leu Ala Thr Lys Leu Asn Ile Leu Val Gln Gln His Phe Asp Leu Ala

<212> PRT

<213> Homo sapien

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70
Ser Thr Thr Ile Thr Asn Ile Pro Met Lys Glu Glu Gln His Ala Asn
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Val Asp Phe Leu Lys Ser Gly Asp Ser His Leu Gly Gly Gly Ser Arg
                       120
Glu Gly Ser Phe Lys Glu Thr Ile Thr Leu Lys Trp Cys Thr Pro Arg
                     135
Thr Asn Asn Ile Glu Leu His Tyr Cys Thr Gly Ala Tyr Arg Ile Ser
                                     155
145 150
Pro Val Asp Val Asn Ser Arg Pro Ser Ser Cys Leu Thr Asn Phe Leu
              165
                                 170
Leu Asn Gly Arg Ser Val Leu Leu Glu Gln Pro Arg Lys Ser Gly Ser
                              185
           180
Lys Val Ile Ser His Met Leu Ser Ser His Gly Gly Glu Ile Phe Leu
                          200
His Val Leu Ser Ser Ser Arg Ser Ile Leu Glu Asp Pro Pro Ser Ile
                     215
                                        220
Ser Glu Gly Cys Gly Gly Arg Val Thr Asp Tyr Arg Ile Thr Asp Phe
                  230
                                  235
Gly Glu Phe Met Arq Gly Lys Gln Ile Asn Ser Phe Ser Thr Pro Gln
                                 250
Ile
     <210> 97
     <211> 128
     <212> PRT
     <213> Homo sapien
     <400> 97
Ser Leu Pro Gln Phe Ala Val His Pro Glu Arg Ser Gly Leu Ala Asp
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Ser Gly Asp Gly Gly Asn Met Ser Val Ala Phe Ala Ala Pro Arg Gln
                              25
Arg Gly Lys Gly Glu Ile Thr Pro Ala Ala Ile Gln Lys Met Leu Asp
                          40
Asp Asn Asn His Leu Ile Gln Cys Ile Met Asp Ser Gln Asn Lys Gly
         55
Lys Thr Ser Glu Cys Ser Gln Tyr Gln Gln Met Leu His Thr Asn Leu
Val Tyr Leu Ala Thr Ile Ala Asp Ser Asn Gln Asn Met Gln Ser Leu
                                 90
Leu Pro Ala Pro Pro Thr Gln Asn Met Pro Met Gly Pro Gly Gly Met
          100
                              105
Asn Gln Ser Gly Pro Pro Pro Pro Pro Arg Ser His Asn Met Pro Ser
                         120
     <210> 98
     <211> 159
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Ala Met Glu Ser Gly Pro Lys Met Leu Ala Pro Val Cys Leu Val Glu
                               25
Asn Asn Asn Glu Gln Leu Leu Val Asn Gln Gln Ala Ile Gln Ile Leu
                           40
Glu Lys Ile Ser Gln Pro Val Val Val Val Ala Ile Val Gly Leu Tyr
                       55
Arg Thr Gly Lys Ser Tyr Leu Met Asn His Leu Ala Gly Gln Asn His
                   70
                                       75
Gly Phe Pro Leu Gly Ser Thr Val Gln Ser Glu Thr Lys Gly Ile Trp
        85
                                   90
Met Trp Cys Val Pro His Pro Ser Lys Pro Asn His Thr Leu Val Leu
                               105
           100
Leu Asp Thr Glu Gly Leu Gly Asp Val Glu Lys Gly Asp Pro Lys Asn
                           120
Asp Ser Trp Ile Phe Ala Leu Ala Val Leu Leu Cys Ser Thr Phe Val
            135
                                140
Tyr Asn Ser Met Ser Thr Ile Asn His Gln Ala Leu Glu Gln Leu
     <210> 99
     <211> 147
     <212> PRT
     <213> Homo sapien
    <400> 99
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Asn Asn Glu Gln Leu Leu Val Asn Gln Gln Ala Ile Gln Ile Leu Glu
                               25
Lys Ile Ser Gln Pro Val Val Val Val Ala Ile Val Gly Leu Tyr Arg
                           40
Thr Gly Lys Ser Tyr Leu Met Asn His Leu Ala Gly Gln Asn His Gly
                       55
Phe Pro Leu Gly Ser Thr Val Gln Ser Glu Thr Lys Gly Ile Trp Met
                   70
                                      75
Trp Cys Val Pro His Pro Ser Lys Pro Asn His Thr Leu Val Leu Leu
               85
                                   90
Asp Thr Glu Gly Leu Gly Asp Val Glu Lys Gly Asp Pro Lys Asn Asp
                              105
Ser Trp Ile Phe Ala Leu Ala Val Leu Leu Cys Ser Thr Phe Val Tyr
       115
                           120
Asn Ser Met Ser Thr Ile Asn His Gln Ala Leu Glu Gln Leu His Tyr
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Val Thr Asp
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     <211> 124
     <212> PRT
     <213> Homo sapien
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                                25
Ile Asn Asp Pro Phe Ile Asp Leu Asn Tyr Met Val Tyr Met Phe Gln
                            40
Tyr Asp Ser Thr His Gly Lys Phe His Gly Thr Val Glu Ala Glu Asn
                        55
Gly Lys Leu Val Ile Asn Gly Asn Pro Ile Thr Ile Phe Gln Glu Arg
                                        75
                    70
Asp Pro Ser Lys Ile Lys Trp Gly Asp Ala Gly Ala Glu Tyr Val Val
                                    90
Glu Ser Thr Gly Val Phe Thr Thr Met Glu Lys Ala Gly Ala His Leu
                                105
            100
Gln Gly Gly Ala Lys Arg Val Ile Ile Ser Ala Pro
                            120
        115
      <210> 101
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      <213> Homo sapien
      <400> 101
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                 5
                                    10
Asp Thr Met Gly Lys Val Lys Val Gly Val Asn Gly Phe Gly Arg Ile
                                25
            20
Gly Arg Leu Val Thr Arg Ala Ala Phe Asn Ser Gly Lys Val Asp Ile
                            40
Val Ala Ile Asn Asp Pro Phe Ile Asp Leu Asn Tyr Met Val Tyr Met
                        55
Phe Gln Tyr Asp Ser Thr His Gly Lys Phe His Gly Thr Val Glu Ala
                    70
                                        75
Glu Asn Gly Lys Leu Val Ile Asn Gly Asn Pro Ile Thr Ile Phe Gln
                                    90
                85
Glu Arg Asp Pro Ser Lys Ile Lys Trp Gly Asp Thr Gly Ala Glu Tyr
            100
                                105
Val Val Glu Ser Thr Gly Val Phe Thr Thr Met Glu Lys Ala Gly
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                            120
        115
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      <400> 102
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gcggagacgg cagccgtgac ggtggcagcg gcggcgcggg acctgggcct gggggaatga
ggcggccgcg gcgggccagc ggcggagccg tgtagcggag aagctccccc tccctgcttc
                                                                       180
                                                                       240
cettggccga gccgggggcg cgcgcgcacg cggccgtcca gagcgggctc cccacccctc
                                                                       300
qactcctqcq acccqcaccq cacccccacc cgggcccgga ggatgatgaa gctcaagtcg
aaccagaccc gcacctacga cggcgacggc tacaagaagc gggccgcatg cctgtgtttc
                                                                       360
cgcagcgaga gcgaggagga ggtgctactc gtgagcagta gtcgccatcc agacagatgg
                                                                       420
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attgtccctg gaggaggcat gtctgtgagg aggctggagt caggagagga agcacaggac tgggaagtt cagttaacat aaagtgctgc agtatcacaa tactcagcca acaatggcac tcgatgtcag gcatcagatg gactgaagtg caaatcttcc ttcaaataag gcatggtgg ttaagtgatg gggctttttc taagtactt tgtgcatgat aggccaacag ccttcccttg ctggccagac gttttcttg gaaaaaaaaa aaaaaaaaaa	aaaaggaca gtatgtctat tggaaggaag acccgtgcag cccagtcgtg actgaagact ctctcaccct cagcaaagaa ttctgtttt ctgtccctcc ccttggattc attttaatt	ttgggaagat gtgctcattg agggaatggt gcatcatatt gccaccacat tcctgtaaga ggctctttcc agggtgtatt attgagggtg ctcttcccac tgaagtgttc	tagttggaat tcactgaagt ttaaaataga ttgaaacatt actcggtttc gaaatggaaa acttctcaca gataatgttg ggggttgggt ccctgcagtc ctgtttgtct	ttttgagaac gctggaagac agacgccata gaggcaaggc tgctcagagc ttggaaacta ggcctcctct ctgtttggtg gtgtaatttg ctctgaagag tatcctgcc	480 540 600 660 720 780 840 900 960 1020 1080 1140 1200 1225
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<400> 103					
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<210> 104 <211> 321 <212> DNA <213> Homo sapi	en				
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<210> 105 <211> 389 <212> DNA <213> Homo sapid	en				
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acatcccaqq caqqacaqaq caqqaqatca tgagatttca tcactcagga tggcttgtga
                                                                       240
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gtgcagtggt gcgatcttgg ctcactgcaa cctctgcctc ctgggttcaa gcagttctcc
                                                                       300
tgcctcagcc tcccaagtag ctgggattac aggcgtccgc caccatgccc agccaatttt
                                                                       360
                                                                       420
tgtactttta gtagagatgg ggtttcacca tgttggccag gctggtctcg aactcctgac
ctcaggtgat ccactcgcct cggcctccca aagtgctggg attataggca tgcgccacca
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                                                                       489
tgcccgggc
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                                                                       120
                                                                       180
tqqaqttcca qqaqcaccac ctqaqtqagg tqcaqaatat ggcatctgag gagaagctgg
                                                                       240
agcaggtgct gagttccatg aaggagaaca aagtggccat cattggaaag attcataccc
                                                                       300
cqatqqaqta taaqqqqqaq ctaqcctcct atqatatqcq gctgagqcgt aagttggact
tatttgccaa cgtaatccat gtgaagtcac ttcctgggta tatgactcgg cacaacaatc
                                                                       360
                                                                       391
tagacctggt gatcattcga gagcagacag a
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      <213> Homo sapien
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Tyr Lys Lys Arg Ala Ala Cys Leu Cys Phe Arg Ser Glu Ser Glu Glu
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                                25
Glu Val Leu Leu Val Ser Ser Ser Arg His Pro Asp Arg Trp Ile Val
                            40
Pro Gly Gly Gly Met Glu Pro Glu Glu Pro Ser Val Ala Ala Val
Arg Glu Val Cys Glu Glu Ala Gly Val Lys Gly Thr Leu Gly Arg Leu
                                        75
                    70
Val Gly Ile Phe Glu Asn Gln Glu Arg Lys His Arg Thr Tyr Val Tyr
                                    90
Val Leu Ile Val Thr Glu Val Leu Glu Asp Trp Glu Asp Ser Val Asn
                                                     110
            100
                                105
Ile Gly Arg Lys Arg Glu Trp Phe Lys Ile Glu Asp Ala Ile Lys Val
                            120
                                                 125
Leu Gln Tyr His Lys Pro Val Gln Ala Ser Tyr Phe Glu Thr Leu Arg
                        135
                                             140
    130
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Gln Gly Tyr Ser Ala Asn Asn Gly Thr Pro Val Val Ala Thr Thr Tyr
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Ser Val Ser Ala Gln Ser Ser Met Ser Gly Ile Arg
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     <211> 247
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Tyr Gln Met Leu Ile Asn Asn Trp Gln Gln Leu Ser Ser Phe Arg Gly
                             25
Gln Glu Phe Val Trp Asp Tyr Val Ile Leu Asp Glu Ala His Lys Ile
                          40
Lys Thr Ser Ser Thr Lys Ser Ala Ile Cys Ala Arg Ala Ile Pro Ala
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Ser Asn Arg Leu Leu Thr Gly Thr Pro Ile Gln Asn Asn Leu Gln
                  70
Glu Leu Trp Ser Leu Phe Asp Phe Ala Cys Gln Gly Ser Leu Leu Gly
                                90
              85
Thr Leu Lys Thr Phe Lys Met Glu Tyr Glu Asn Pro Ile Thr Arg Ala
         100 105
Arg Glu Lys Asp Ala Thr Pro Gly Glu Lys Ala Leu Gly Phe Lys Ile
                                125
       115
                         120
Ser Glu Asn Leu Met Ala Ile Ile Lys Pro Tyr Phe Leu Arg Arg Thr
                      135
Lys Glu Asp Val Gln Lys Lys Ser Ser Asn Pro Glu Ala Arg Leu
                  150
                                     155
Asn Glu Lys Asn Pro Asp Val Asp Ala Ile Cys Glu Met Pro Ser Leu
                                 170
        165
Ser Arg Arg Asn Asp Leu Ile Ile Trp Ile Arg Leu Val Pro Leu Gln
          180 185 190
Glu Glu Ile Tyr Arg Lys Phe Val Ser Leu Asp His Ile Lys Glu Leu
                         200
Leu Met Glu Thr Arg Ser Pro Leu Ala Glu Leu Gly Val Leu Lys Lys
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                                        220
Leu Cys Asp His Pro Arg Leu Leu Ser Ala Arg Ala Cys Cys Leu Leu
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Asn Leu Gly Thr Phe Ser Ala
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     <210> 113
     <211> 107
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Lys Asp Gln Gln Pro Gln Met Glu Leu Pro Leu Gln Gly Cys Asn Ile
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25

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Thr Tyr Ile Pro Lys Asp Ser Lys Lys Lys His Glu Leu Lys Ile
                            40
Thr Gln Gln Gly Thr Asp Pro Leu Val Leu Ala Val Gln Ser Lys Glu
                        55
Gln Ala Glu Gln Trp Leu Lys Val Ile Lys Glu Ala Tyr Ser Gly Cys
                                       75
                   70
Ser Gly Pro Val Asp Ser Glu Cys Pro Pro Pro Pro Ser Ser Pro Val
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His Lys Ala Glu Leu Glu Lys Lys Leu Ser Ser
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      <211> 155
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Asp Lys Asn Glu Ile Ala Ser Val Ala Tyr Arg Tyr Arg Arg Trp Lys
                               25
Leu Gly Asp Asp Ile Asp Leu Ile Val Arg Cys Glu His Asp Gly Val
                           40
Met Thr Gly Ala Asn Gly Glu Val Ser Phe Ile Asn Ile Lys Thr Leu
                       5.5
Asn Glu Trp Asp Ser Arg His Cys Asn Gly Val Asp Trp Arg Gln Lys
                   70
                                       75
Leu Asp Ser Gln Arg Gly Ala Val Ile Ala Thr Glu Leu Lys Asn Asn
                                    90
                85
Ser Tyr Lys Leu Ala Arg Trp Thr Cys Cys Ala Leu Leu Ala Gly Ser
                                105
Glu Tyr Leu Lys Leu Gly Tyr Val Ser Arg Tyr His Val Lys Asp Ser
       115
                           120
Ser Arg His Val Ile Leu Gly Thr Gln Gln Phe Lys Pro Asn Glu Phe
                       135
Ala Ser Gln Ile Asn Leu Ser Val Glu Asn Ala
                   150
      <210> 115
      <211> 129
      <212> PRT
      <213> Homo sapien
      <400> 115
Gly Val Arg Trp Leu Thr Arg Ala Leu Val Ser Ala Gly Asn Pro Gly
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Ala Trp Arg Gly Leu Ser Thr Ser Ala Ala Ala His Ala Ala Ser Arg
                               25
Ser Gln Ala Ala Val Pro Val Glu Phe Gln Glu His His Leu Ser
                           40
Glu Val Gln Asn Met Ala Ser Glu Glu Lys Leu Glu Gln Val Leu Ser
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                                           60
Ser Met Lys Glu Asn Lys Val Ala Ile Ile Gly Lys Ile His Thr Pro
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<212> DNA

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Lys Leu Asp Leu Phe Ala Asn Val Ile His Val Lys Ser Leu Pro Gly
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Tyr Met Thr Arg His Asn Asn Leu Asp Leu Val Ile Ile Arg Glu Gln
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Thr
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                                                                       120
tggctcaccg ctgcctagag ccaaggaget catcctgaat gacettcccg ccagcactce
                                                                       180
                                                                       240
tgcctccaaa tcctgtgact cctccccgcc ccaggacgct tccaccccca ggcccagctc
                                                                       300
ggccagtcac ctctgccagc ttgctgccaa gccagcacct tccacggaca gcgtcgccct
gaggagecee etgactetgt ecagtecett caccaegtee tteageetgg geteceacag
                                                                       360
                                                                       420
cacteteaac ggagacetet eegtgeeeag eteetaegte ageeteeace tgteeecea
                                                                       480
ggtcagcagc tctgtggtgt acggacgctc ccccgtgatg gcatttgagt ctcatcccca
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tctccqaqqq tcatccqtct cttcctccct acccagcatc cctgggggaa agccggccta
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ctccttccac
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      <211> 154
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aggetttttt ggteceattt gtgagattga tgttgeeett aatgatgggg aaaccaggaa
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                                                                       154
aatggcagaa atgaaaactg aggatggcaa agta
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      <211> 449
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cgcgcgctgg tgtcggcgca atgggtggcg gaggcgctgc gggccccgcg cgctgggcag
                                                                       120
cetetgeage tgetggaege etectggtae etgeegaage tggggegega egegegaege
                                                                       180
qaqttcqaqq aqcqccacat cccqqqcqcc qctttcttcg acatcgacca gtgcagcgac
                                                                       240
                                                                       300
cgcacctcgc cctacgacca catgctgccc ggggccgagc atttcgcgga gtacgcaggc
                                                                       360
cgcctgggcg tgggcgcggc cacccacgtc gtgatctacg acgccagcga ccagggcctc
tactccgccc cgcgcgtctg gtggatgttc cgcgccttcg gccaccacgc cgtgtcactg
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cttgatggcg gcctccgcca ctggctgcg
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      <210> 119
      <211> 642
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### <213> Homo sapien

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<400>	119											
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<213>	Homo sap	pien										
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	Homo say	pien										
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Cys Ile Pro	Ala Arg 20	Arg Asp	Leu	Val 25	Asp	Ser	Pro	Ala	Ser 30	Leu	Ala	
Ser Ser Leu 35	Gly Ser	Pro Leu	Pro 40	Arg	Ala	Lys	Glu	Leu 45	Ile	Leu	Asn	
Asp Leu Pro 50	Ala Ser	Thr Pro	Ala	Ser	Lys	Ser	Cys 60	Asp	Ser	Ser	Pro	
Pro Gln Asp 65	Ala Ser	Thr Pro	Arg	Pro	Ser	Ser 75	Ala	Ser	His	Leu	Cys 80	
Gln Leu Ala	Ala Lys 85	Pro Ala	Pro	Ser	Thr 90	Asp	Ser	Val	Ala	Leu 95	Arg	
Ser Pro Leu	Thr Leu 100	Ser Ser	Pro	Phe 105	Thr	Thr	Ser	Phe	Ser 110	Leu	Gly	
			_	_	~		_	~	~	-	** 7	

Ser His Ser Thr Leu Asn Gly Asp Leu Ser Val Pro Ser Ser Tyr Val

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120
       115
Ser Leu His Leu Ser Pro Gln Val Ser Ser Ser Val Val Tyr Gly Arg
                                  140
                       135
Ser Pro Val Met Ala Phe Glu Ser His Pro His Leu Arg Gly Ser Ser
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145 150
Val Ser Ser Ser Leu Pro Ser Ile Pro Gly Gly Lys Pro Ala Tyr Ser
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Phe His
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     <211> 36
     <212> PRT
     <213> Homo sapien
     <400> 122
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Asp Gly Lys Val
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     <211> 136
     <212> PRT
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                               25
Asp Ala Ser Trp Tyr Leu Pro Lys Leu Gly Arg Asp Ala Arg Arg Glu
                          40
Phe Glu Glu Arg His Ile Pro Gly Ala Ala Phe Phe Asp Ile Asp Gln
                       55
Cys Ser Asp Arg Thr Ser Pro Tyr Asp His Met Leu Pro Gly Ala Glu
                   70
                                      75
His Phe Ala Glu Tyr Ala Gly Arg Leu Gly Val Gly Ala Ala Thr His
              85
                                  90
Val Val Ile Tyr Asp Ala Ser Asp Gln Gly Leu Tyr Ser Ala Pro Arg
                              105
Val Trp Trp Met Phe Arg Ala Phe Gly His His Ala Val Ser Leu Leu
                           120
Asp Gly Gly Leu Arg His Trp Leu
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     <210> 124
     <211> 133
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     <213> Homo sapien
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                              25
Gly Ala Pro His Asn Pro Ala Pro Pro Thr Ser Thr Val Ile His Ile
                          40
Arg Ser Glu Thr Ser Val Pro Asp His Val Val Trp Ser Leu Phe Asn
                      55
Thr Leu Phe Met Asn Pro Cys Cys Leu Gly Phe Ile Ala Phe Ala Tyr
                                     75
                   70
Ser Val Lys Ser Arg Asp Arg Lys Met Val Gly Asp Val Thr Gly Ala
                      90
              85
Gln Ala Tyr Ala Ser Thr Ala Lys Cys Leu Asn Ile Trp Ala Leu Ile
                             105
Leu Gly Ile Leu Met Thr Ile Leu Leu Ile Val Ile Pro Val Leu Ile
                          120
       115
Phe Gln Ala Tyr Gly
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Ser Thr Pro Gly Thr Ala Pro Pro Pro Lys Val Leu Thr Ser Pro Ala
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           20
Thr Thr Pro Met Ser Thr Met Ser Thr Ile His Thr Ser Ser Thr Pro
                           40
Glu Thr Thr His Thr Ser Thr Val Leu Thr Thr Thr Ala Thr Met Thr
                   55
Arg Ala Thr Asn Ser Thr Ala Thr Pro Ser Ser Thr Leu Gly Thr Thr
                  70
                                     75
Arg Ile Leu Thr Glu Leu Thr Thr Thr Ala Thr Thr Thr Ala Ala Thr
              85
                                  90
Gly Ser Thr Ala Thr Leu Ser Ser Thr Pro Gly Thr Thr Trp Ile Leu
          100
                              105
Thr Glu Pro Ser Thr Ile Ala Thr Val Met Val Pro Thr Gly Ser Thr
                                             125
                          120
Ala Thr Ala Ser Ser Thr Leu Gly Thr Ala His Thr Pro Lys Val Val
                      135
Thr Thr Met Ala Thr Met Pro Thr Ala Thr Ala Ser Thr Val Pro Ser
                   150
                                      155
Ser Ser Thr Val Gly Thr Thr Arg Thr Pro Ala Val Leu Pro Ser Ser
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Leu Pro Thr Phe Ser Val Ser Thr Val Ser Ser Ser Val Leu Thr Thr
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Leu Arg Pro
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     <211> 509
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<210> 128 <211> 500 <212> DNA <213> Homo sapie:	n				
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cactgtagtg ggtgttggac tctggctgat gaacttgctc ggatctgcag catgggagct ttctgtgacc gccaattcta ggagagtcgg ctcaatctgg gatcgtcaag tacagtcctg acctgtatgt acctgga	ttgtggatgt tatttcttca agattgtagt tgcagagaaa	tttggaagat gacacctaaa ggtaactgca tgttaatgtc	aagcttaaag attgtggcag ggagtccgtc ttcaaattca	gagaaatgat ataaagatta agcaagaagg ttattcctca	180 240 300 360 420 480 497
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<210> 131 <211> 509 <212> DNA <213> Homo sapi	en				
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		tatagcaaaa				300
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Val Thr Leu Leu Tyr Asp Leu Val Thr Glu Lys Met Phe Ala Glu Glu 85 90 95	
Glu Ala Glu Leu Thr Gln Glu Met Ser Pro Glu Lys Leu Gln Gln Tyr 100 105 110	
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Ile Thr Ala His Leu Leu Ala Leu Pro Glu His Asp Ala Arg Glu Lys 130 135 140	
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Lys Glu Lys Asn Ile Lys Arg Gly Gly Asn Arg Phe Glu Pro Tyr Ser
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Asn Pro Thr Lys Arg Tyr Arg Ala Phe Ile Thr Asn Ile Pro Phe Asp
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Val Thr Tyr Val Glu Leu Leu Met Asp Ala Glu Gly Lys Ser Arg Gly
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Cys Ala Val Val Glu Phe Lys Met Glu Glu Ser Met Lys Lys Ala Ala
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Glu Asp Pro Asp Gly Glu His Ala Arg Arg Ala Met Gln Lys Ala Gly
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Trp Lys Lys Leu Lys Glu Val Phe Ser Met Ala Gly Val Val Val Arg
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Ala Asp Ile Leu Glu Asp Lys Asp Gly Lys Ser Arg Gly Ile Gly Ile
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Val Thr Phe Glu Gln Ser Ile Glu Ala Val Gln Ala Ile Ser Met Phe
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His Leu Asn Pro Asp Gln Leu Glu Ala Val Glu Lys Tyr Glu Glu Val

55

- Parties and the same

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His Met Leu Lys Leu Glu Ala Glu Lys Lys Leu Arg Thr Ile Leu
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                           40
Lys Thr Glu Ser Val Lys Glu Ser Glu Ser Leu Met Glu Phe Ala Gln
Pro Glu Ile Gln Pro Gln Glu Phe Leu Asn Arg Arg Tyr Met Thr Glu
                   70
                                      75
Val Asp Tyr Ser Asn Lys Gln Gly Glu Glu Gln Pro Trp Glu Ala Asp
                                  90
Tyr Ala Arg Lys Pro Asn Leu Pro Lys Arg Trp Asp Met Leu Thr Glu
                              105
           100
Pro Asp Gly Gln Glu Lys Lys Gln Glu Ser Phe Lys Ser Trp Glu Ala
                                              125
                          120
       115
Ser Gly Lys His Gln Glu Val Ser Lys Pro Ala Val Ser Leu Glu Gln
                                          140
                      135
Arg Lys Gln Asp Thr Ser Lys Leu Arg Ser Thr Leu Pro Glu Glu Gln
                   150
                                     155
Lys Lys Gln Glu Ile Ser Lys Ser Lys Pro Ser Pro Ser Gln Trp Lys
                                   170
Gln Asp Thr Pro Lys Ser Lys Ala Gly Tyr Val Gln Glu Glu Gln Lys
                               185
           180
Lys Gln Glu Thr Pro Lys Leu Trp Pro Val Gln Leu Gln Lys Glu Gln
                          200
Asp Pro Lys Lys Gln Thr Pro Lys Ser Trp Thr Pro Ser Met Gln Ser
                               220
                       215
Glu Gln Asn Thr Thr Lys Ser Trp Thr Thr Pro Met Cys Glu Glu Gln
                                   235
                   230
Asp Ser Lys Gln Pro Glu Thr Pro Lys Ser Trp Glu Asn Asn Val Glu
```

Ser Gln Lys His Ser Leu Thr Ser Gln Ser Gln Ile Ser Pro Lys Ser Trp Gly Val Ala Thr Ala Ser Leu Ile Pro Asn Asp Gln Leu Leu Pro Arg Lys Leu Asn Thr Glu Pro Lys Asp Val Pro Lys Pro Val His Gln Pro Val Gly Ser Ser Ser Thr Leu Pro Lys Asp Pro Val Leu Arg Lys Glu Lys Leu Gln Asp Leu Met Thr Gln Ile Gln Gly Thr Cys Asn Phe Met Gln Glu Ser Val Leu Asp Phe Asp Lys Pro Ser Ser Ala Ile Pro Thr Ser Gln Pro Pro Ser Ala Thr Pro Gly Ser Pro Val Ala Ser Lys Glu Gln Asn Leu Ser Ser Gln Ser Asp Phe Leu Gln Glu Pro Leu Gln Val Phe Asn Val Asn Ala Pro Leu Pro Pro Arg Lys Glu Gln Glu Ile Lys Glu Ser Pro Tyr Ser Pro Gly Tyr Asn Gln Ser Phe Thr Thr Ala Ser Thr Gln Thr Pro Pro Gln Cys Gln Leu Pro Ser Ile His Val Glu Gln Thr Val His Ser Gln Glu Thr Ala Ala Asn Tyr His Pro Asp Gly Thr Ile Gln Val Ser Asn Gly Ser Leu Ala Phe Tyr Pro Ala Gln Thr Asn Val Phe Pro Arg Pro Thr Gln Pro Phe Val Asn Ser Arg Gly Ser Val Arg Gly Cys Thr Arg Gly Gly Arg Leu Ile Thr Asn Ser Tyr Arg Ser Pro Gly Gly Tyr Lys Gly Phe Asp Thr Tyr Arg Gly Leu Pro Ser Ile Ser Asn Gly Asn Tyr Ser Gln Leu Gln Phe Gln Ala Arg Glu Tyr Ser Gly Ala Pro Tyr Ser Gln Arg Asp Asn Phe Gln Gln Cys Tyr Lys Arg Gly Gly Thr Ser Gly Gly Pro Arg Ala Asn Ser Arg Ala Gly Trp Ser Asp Ser Ser Gln Val Ser Ser Pro Glu Arg Asp Asn Glu Thr Phe Asn Ser Gly Asp Ser Gly Gln Gly Asp Ser Arg Ser Met Thr Pro Val Asp Val Pro Val Thr Asn Pro Ala Ala Thr Ile Leu Pro Val His Val Tyr Pro Leu Pro Gln Gln Met Arg Val Ala Phe Ser Ala Ala Arg Thr Ser Asn Leu Ala Pro Gly Thr Leu Asp Gln Pro Ile Val Phe Asp Leu Leu Leu Asn Asn Leu Gly Glu Thr Phe Asp Leu Gln Leu Gly Arg Phe Asn Cys Pro Val Asn Gly Thr Tyr Val Phe Ile Phe His Met Leu Lys Leu Ala Val Asn Val Pro Leu Tyr Val Asn Leu Met Lys Asn Glu Glu 

```
Val Leu Val Ser Ala Tyr Ala Asn Asp Gly Ala Pro Asp His Glu Thr
                     695
Ala Ser Asn His Ala Ile Leu Gln Leu Phe Gln Gly Asp Gln Ile Trp
                         715
                710
Leu Arg Leu His Arg Gly Ala Ile Tyr Gly Ser Ser Trp Lys Tyr Ser
                     730
           725
Thr Phe Ser Gly Tyr Leu Leu Tyr Gln Asp
     <210> 186
     <211> 705
     <212> PRT
     <213> Homo sapien
     <400> 186
Ala Leu Leu Asn Val Arg Gln Pro Pro Ser Thr Thr Thr Phe Val Leu
                               10
Asn Gln Ile Asn His Leu Pro Pro Leu Gly Ser Thr Ile Val Met Thr
                            25
    20
Lys Thr Pro Pro Val Thr Thr Asn Arg Gln Thr Ile Thr Leu Thr Lys
                                          45
                        40
Phe Ile Gln Thr Thr Ala Ser Thr Arg Pro Ser Val Ser Ala Pro Thr
                     55
Val Arg Asn Ala Met Thr Ser Ala Pro Ser Lys Asp Gln Val Gln Leu
                        75
Lys Asp Leu Leu Lys Asn Asn Ser Leu Asn Glu Leu Met Lys Leu Lys
                                90
           85
Pro Pro Ala Asn Ile Ala Gln Pro Val Ala Thr Ala Ala Thr Asp Val
          100
                             105
Ser Asn Gly Thr Val Lys Lys Glu Ser Ser Asn Lys Glu Gly Ala Arg
                        120
Met Trp Ile Asn Asp Met Lys Met Arg Ser Phe Ser Pro Thr Met Lys
                     135
                                      140
Val Pro Val Val Lys Glu Asp Asp Glu Pro Glu Glu Glu Asp Glu Glu
                                   155
                 150
Glu Met Gly His Ala Glu Thr Tyr Ala Glu Tyr Met Pro Ile Lys Leu
                                170 175
             165
Lys Ile Gly Leu Arg His Pro Asp Ala Val Val Glu Thr Ser Ser Leu
                            185 190
Ser Ser Val Thr Pro Pro Asp Val Trp Tyr Lys Thr Ser Ile Ser Glu
                         200
Glu Thr Ile Asp Asn Gly Trp Leu Ser Ala Leu Gln Leu Glu Ala Ile
                                        220
                      215
Thr Tyr Ala Ala Gln Gln His Glu Thr Phe Leu Pro Asn Gly Asp Arg
                                    235
                 230
Ala Gly Phe Leu Ile Gly Asp Gly Ala Gly Val Gly Lys Gly Arg Thr
              245
                   250
Ile Ala Gly Ile Ile Tyr Glu Asn Tyr Leu Leu Ser Arg Lys Arg Ala
                            265
          260
Leu Trp Phe Ser Val Ser Asn Asp Leu Lys Tyr Asp Ala Glu Arg Asp
                                          285
                         280
       275
Leu Arg Asp Ile Gly Ala Lys Asn Ile Leu Val His Ser Leu Asn Lys
                  295
                                       300
```

Phe Lys Tyr Gly Lys Ile Ser Ser Lys His Asn Gly Ser Val Lys Lys

305					310					315					320
Gly	Val	Ile	Phe			Tyr	Ser	Ser	Leu 330		Gly	Glu	Ser	Gln 335	
Gly	Gly	Lys		325 Lys	Thr	Arg	Leu			Leu	Leu	His	Trp		Gly
Asp	Asp		340 Asp	Gly	Val	Ile		345 Phe	Asp	Glu	Cys	His	Lys	Ala	Lys
Asn		355 Cys	Pro	Val	Gly		360 Ser	Lys	Pro	Thr		365 Thr	Gly	Leu	Ala
Val	370 Leu	Glu	Leu	Gln		375 Lys	Leu	Pro	Lys		380 Arg	Val	Val	Tyr	
385 Ser	Ala	Thr	Gly	Ala	390 Ser	Glu	Pro	Arg		395 Met	Ala	Tyr	Met		400 Arg
Leu	Gly	Ile	Trp	405 Gly	Glu	Gly	Thr	Pro	410 Phe	Arg	Glu	Phe	Ser	415 Asp	Phe
Ile	Gln	Ala	420 Val	Glu	Arg	Arg	Gly	425 Val	Gly	Ala	Met	Glu	430 Ile	Val	Ala
		435					440					445	Leu		
	450					455					460		Gln		
465					470					475			Ala		480
	_			485					490					495	
_			500					505					Arg 510		
_		515					520					525	Phe		
-	530					535					540		Leu		
545					550					555			Gln		560
				565					570				Gly	575	
			580					585					Leu 590		
		595					600					605	Leu		
Ile	Asp 610		Thr	Ala		Ser 615		Asn		Ser			Asp	Ser	Pro
Cys 625	Lys	Glu	Asn	Lys	Ile 630	Lys	Lys	Arg	Lys	Gly 635	Glu	Glu	Ile	Thr	Arg 640
	Ala	Lys	Lys	Ala 645	Arg	Lys	Val	Gly	Gly 650	Leu	Thr	Gly	Ser	Ser 655	Ser
Asp	Asp	Ser	Gly 660		Glu	Ser	Asp	Ala 665	Ser	Asp	Asn	Glu	Glu 670	Ser	Asp
Tyr	Glu	Ser 675		Lys	Asn	Met	Ser 680		Gly	Asp	Asp	Asp 685	Asp	Phe	Asn
Pro	Phe 690		Asp	Glu	Ser	Asn 695		Asp	Asp	Glu	Asn 700		Pro	Trp	Leu
Ile 705	090					0,0					, 00				

<210> 187 <211> 595 <212> PRT <213> Homo sapien

<400> 187 Glu Ser Pro Arg His Arg Gly Glu Gly Gly Glu Trp Gly Pro Gly 10 Val Pro Arg Glu Arg Arg Glu Ser Ala Gly Glu Trp Gly Ala Asp Thr 25 Pro Lys Glu Gly Gly Glu Ser Ala Gly Glu Trp Gly Ala Glu Val Pro 40 Arg Gly Arg Gly Glu Gly Ala Gly Glu Trp Gly Pro Asp Thr Pro Lys Glu Arg Gly Gln Gly Val Arg Glu Trp Gly Pro Glu Ile Pro Gln Glu 75 70 His Gly Glu Ala Thr Arg Asp Trp Ala Leu Glu Ser Pro Arg Ala Leu Gly Glu Asp Ala Arg Glu Leu Gly Ser Ser Pro His Asp Arg Gly Ala 105 Ser Pro Arg Asp Leu Ser Gly Glu Ser Pro Cys Thr Gln Arg Ser Gly 120 Leu Leu Pro Glu Arg Arg Gly Asp Ser Pro Trp Pro Pro Trp Pro Ser 135 140 Pro Gln Glu Arg Asp Ala Gly Thr Arg Asp Arg Glu Glu Ser Pro Arg 155 150 Asp Trp Gly Gly Ala Glu Ser Pro Arg Gly Trp Glu Ala Gly Pro Arg 170 165 Glu Trp Gly Pro Ser Pro Ser Gly His Gly Asp Gly Pro Arg Arg Arg 185 Pro Arg Lys Arg Arg Gly Arg Lys Gly Arg Met Gly Arg Gln His Glu 200 195 Ala Ala Ala Thr Ala Ala Thr Ala Ala Thr Ala Thr Gly Gly Thr Ala 220 215 Glu Glu Ala Gly Ala Ser Ala Pro Glu Ser Gln Ala Gly Gly Gro 230 235 Arg Gly Arg Ala Arg Gly Pro Arg Gln Gln Gly Arg Arg Arg His Gly 250 245 Thr Gln Arg Arg Arg Gly Pro Pro Gln Ala Arg Glu Glu Gly Pro Arg 265 260 Asp Ala Thr Thr Ile Leu Gly Leu Gly Thr Pro Ser Gly Glu Gln Arg 280 Ala Asp Gln Ser Gln Ala Leu Pro Ala Leu Ala Gly Ala Ala Ala Ala 295 His Ala His Ala Ile Pro Gly Ala Gly Pro Ala Ala Ala Pro Val Gly 310 Gly Arg Gly Arg Arg Gly Gly Trp Arg Gly Gly Arg Arg Gly Gly Ser 330 325 Ala Gly Ala Gly Gly Gly Arg Gly Gly Arg Gly Arg Gly Arg Gly 345 Gly Gly Arg Gly Gly Gly Ala Gly Arg Gly Gly Ala Ala Gly 360 Pro Arg Glu Gly Ala Ser Ser Pro Gly Ala Arg Arg Gly Glu Gln Arg 375 380 Arg Arg Gly Arg Gly Pro Pro Ala Ala Gly Ala Ala Gln Val Ser Ala 395 390

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Arg Gly Arg Arg Ala Arg Gly Gln Arg Ala Gly Glu Glu Ala Gln Asp
                                  410
Gly Leu Leu Pro Arg Gly Arg Asp Arg Leu Pro Leu Arg Pro Gly Asp
                              425
Ala Asn Gln Arg Ala Glu Arg Pro Gly Pro Pro Arg Gly Gly His Gly
                         440
Pro Val Asn Ala Ser Ser Ala Pro Asp Thr Ser Pro Pro Arg His Pro
                                         460
                      455
Arg Arg Trp Val Ser Gln Gln Arg Gln Arg Leu Trp Arg Gln Phe Arg
                                     475
                  470
Val Gly Gly Gly Phe Pro Pro Pro Pro Pro Ser Arg Pro Pro Ala Val
                                 490
Leu Leu Pro Leu Leu Arg Leu Ala Cys Ala Gly Asp Pro Gly Ala Thr
                              505
           500
Arg Pro Gly Pro Arg Arg Pro Ala Arg Arg Pro Arg Gly Glu Leu Ile
                                              525
                          520
       515
Pro Arg Arg Pro Asp Pro Ala Ala Pro Ser Glu Glu Gly Leu Arg Met
                                          540
         535
Glu Ser Ser Val Asp Asp Gly Ala Thr Ala Thr Thr Ala Asp Ala Ala
                                      555
                  550
Ser Gly Glu Ala Pro Glu Ala Gly Pro Ser Pro Ser His Ser Pro Thr
                                 570
              565
Met Cys Gln Thr Gly Gly Pro Gly Pro Pro Pro Pro Gln Pro Pro Arg
  580
                              585
Trp Leu Pro
       595
      <210> 188
      <211> 376
      <212> PRT
      <213> Homo sapien
      <400> 188
Glu Met Arg Lys Phe Asp Val Pro Ser Met Glu Ser Thr Leu Asn Gln
                                  10
Pro Ala Met Leu Glu Thr Leu Tyr Ser Asp Pro His Tyr Arg Ala His
                               25
           20
Phe Pro Asn Pro Arg Pro Asp Thr Asn Lys Asp Val Tyr Lys Val Leu
                           40
Pro Glu Ser Lys Lys Ala Pro Gly Ser Gly Ala Val Phe Glu Arg Asn
                                          60
                       55
Gly Pro His Ala Ser Ser Ser Gly Val Leu Pro Leu Gly Leu Gln Pro
                                      75
                   70
Ala Pro Gly Leu Ser Lys Ser Leu Ser Ser Gln Val Trp Gln Pro Ser
                                   90
               85
Pro Asp Pro Trp His Pro Gly Glu Gln Ser Cys Glu Leu Ser Thr Cys
                              105
Arg Gln Gln Leu Glu Leu Ile Arg Leu Gln Met Glu Gln Met Gln Leu
                          120
Gln Asn Gly Ala Met Cys His His Pro Ala Ala Phe Ala Pro Leu Leu
                                          140
                       135
Pro Thr Leu Glu Pro Ala Gln Trp Leu Ser Ile Leu Asn Ser Asn Glu
145 150 155 160
His Leu Leu Lys Glu Lys Glu Leu Leu Ile Asp Lys Gln Arg Lys His
```

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165
                                    170
Ile Ser Gln Leu Glu Gln Lys Val Arg Glu Ser Glu Leu Gln Val His
            180
                               185
Ser Ala Leu Leu Gly Arg Pro Ala Pro Phe Gly Asp Val Cys Leu Leu
                        200
Arg Leu Gln Glu Leu Gln Arg Glu Asn Thr Phe Leu Arg Ala Gln Phe
                    215
                                           220
Ala Gln Lys Thr Glu Ala Leu Ser Lys Glu Lys Met Glu Leu Glu Lys
                   230
                               235
Lys Leu Ser Ala Ser Glu Val Glu Ile Gln Leu Ile Arg Glu Ser Leu
                245
                                   250
Lys Val Thr Leu Gln Lys His Ser Glu Glu Gly Lys Lys Gln Glu Glu
                                265
Arg Val Lys Gly Arg Asp Lys His Ile Asn Asn Leu Lys Lys Cys
        275
                            280
Gln Lys Glu Ser Glu Gln Asn Arg Glu Lys Gln Gln Arg Ile Glu Thr
                       295
                                           300
Leu Glu Arg Tyr Leu Ala Asp Leu Pro Thr Leu Glu Asp His Gln Lys
                   310
                                       315
Gln Thr Glu Gln Leu Lys Asp Ala Glu Leu Lys Asn Thr Glu Leu Gln
               325
                                   330
Glu Arg Val Ala Glu Leu Glu Thr Leu Leu Glu Asp Thr Gln Ala Thr
           340
                               345
Cys Arg Glu Lys Glu Val Gln Leu Glu Ser Leu Arg Gln Arg Glu Ala
       355
                           360
Asp Leu Ser Ser Ala Arg His Arg
   370
      <210> 189
      <211> 160
      <212> PRT
      <213> Homo sapien
      <400> 189
Met Leu Glu Ala His Arg Arg Gln Arg His Pro Phe Leu Leu Gly
                                   10
Thr Thr Ala Asn Arg Thr Gln Ser Leu Asn Tyr Gly Cys Ile Val Glu
                               25
Asn Pro Gln Thr His Glu Val Leu His Tyr Val Glu Lys Pro Ser Thr
                           40
Phe Ile Ser Asp Ile Ile Asn Cys Gly Ile Tyr Leu Phe Ser Pro Glu
Ala Leu Lys Pro Leu Arg Asp Val Phe Gln Arg Asn Gln Gln Asp Gly
                   70
                                       75
Gln Leu Glu Asp Ser Pro Gly Leu Trp Pro Gly Ala Gly Thr Ile Arg
                                   90
Leu Glu Gln Asp Val Phe Ser Ala Leu Ala Gly Gln Gly Gln Ile Tyr
           100
                              105
Val His Leu Thr Asp Gly Ile Trp Ser Gln Ile Lys Ser Ala Gly Ser
                          120
Ala Leu Tyr Ala Ser Arg Leu Tyr Leu Ser Arg Tyr Gln Asp Thr His
                       135
                                          140
Pro Glu Arg Leu Ala Lys His Thr Pro Gly Gly Pro Trp Ile Arg Gly
145
                   150
```

<210> 190

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<211> 146
      <212> PRT
      <213> Homo sapien
      <400> 190
Met Asp Pro Arg Ala Ser Leu Leu Leu Leu Gly Asn Val Tyr Ile His
                                   10
Pro Thr Ala Lys Val Ala Pro Ser Ala Val Leu Gly Pro Asn Val Ser
                                25
Ile Gly Lys Gly Val Thr Val Gly Glu Gly Val Arg Leu Arg Glu Ser
                            40
Ile Val Leu His Gly Ala Thr Leu Gln Glu His Thr Cys Val Leu His
                        55
Ser Ile Val Gly Trp Gly Ser Thr Val Gly Arg Trp Ala Arg Val Glu
                    70
                                        75
Gly Thr Pro Ser Asp Pro Asn Pro Asn Asp Pro Arg Ala Arg Met Asp
               85
                                   90
Ser Glu Ser Leu Phe Lys Asp Gly Lys Leu Leu Pro Ala Ile Thr Ile
                               105
Leu Gly Cys Arg Val Arg Ile Pro Ala Glu Val Leu Ile Leu Asn Ser
       115
                         120
                                               125
Ile Val Leu Pro His Lys Glu Leu Ser Arg Ser Phe Thr Asn Gln Ile
                        135
Ile Leu
145
      <210> 191
      <211> 704
      <212> PRT
      <213> Homo sapien
      <400> 191
Glu Gly Gly Cys Ala Ala Gly Arg Gly Arg Glu Leu Glu Pro Glu Leu
                                    10
Glu Pro Gly Pro Gly Pro Gly Ser Ala Leu Glu Pro Gly Glu Glu Phe
            2.0
                                25
Glu Ile Val Asp Arg Ser Gln Leu Pro Gly Pro Gly Asp Leu Arg Ser
                           4.0
Ala Thr Arg Pro Arg Ala Ala Glu Gly Trp Ser Ala Pro Ile Leu Thr
Leu Ala Arg Arg Ala Thr Gly Asn Leu Ser Ala Ser Cys Gly Ser Ala
Leu Arg Ala Ala Gly Leu Gly Gly Gly Asp Ser Gly Asp Gly Thr
                                   90
Ala Arg Ala Ala Ser Lys Cys Gln Met Met Glu Glu Arg Ala Asn Leu
           100
                               105
Met His Met Met Lys Leu Ser Ile Lys Val Leu Leu Gln Ser Ala Leu
                           120
                                               125
Ser Leu Gly Arg Ser Leu Asp Ala Asp His Ala Pro Leu Gln Gln Phe
                      135
                                           140
Phe Val Val Met Glu His Cys Leu Lys His Gly Leu Lys Val Lys
                   150
                                       155
```

Ser Phe Ile Gly Gln Asn Lys Ser Phe Phe Gly Pro Leu Glu Leu Val Glu Lys Leu Cys Pro Glu Ala Ser Asp Ile Ala Thr Ser Val Arg Asn Leu Pro Glu Leu Lys Thr Ala Val Gly Arg Gly Arg Ala Trp Leu Tyr Leu Ala Leu Met Gln Lys Lys Leu Ala Asp Tyr Leu Lys Val Leu Ile Asp Asn Lys His Leu Leu Ser Glu Phe Tyr Glu Pro Glu Ala Leu Met Met Glu Glu Gly Met Val Ile Val Gly Leu Leu Val Gly Leu Asn Val Leu Asp Ala Asn Leu Cys Leu Lys Gly Glu Asp Leu Asp Ser Gln Val Gly Val Ile Asp Phe Ser Leu Tyr Leu Lys Asp Val Gln Asp Leu Asp Gly Gly Lys Glu His Glu Arg Ile Thr Asp Val Leu Asp Gln Lys Asn Tyr Val Glu Glu Leu Asn Arg His Leu Ser Cys Thr Val Gly Asp Leu Gln Thr Lys Ile Asp Gly Leu Glu Lys Thr Asn Ser Lys Leu Gln Glu Glu Leu Ser Ala Ala Thr Asp Arg Ile Cys Ser Leu Gln Glu Glu Gln Gln Gln Leu Arg Glu Gln Asn Glu Leu Ile Arg Glu Arg Ser Glu Lys Ser Val Glu Ile Thr Lys Gln Asp Thr Lys Val Glu Leu Glu Thr Tyr Lys Gln Thr Arg Gln Gly Leu Asp Glu Met Tyr Ser Asp Val Trp Lys Gln Leu Lys Glu Glu Lys Lys Val Arg Leu Glu Leu Glu Lys Glu Leu Glu Leu Gln Ile Gly Met Lys Thr Glu Met Glu Ile Ala Met Lys Leu Leu Glu Lys Asp Thr His Glu Lys Gln Asp Thr Leu Val Ala Leu Arg Gln Gln Leu Glu Glu Val Lys Ala Ile Asn Leu Gln Met Phe His Lys Ala Gln Asn Ala Glu Ser Ser Leu Gln Gln Lys Asn Glu Ala Ile Thr Ser Phe Glu Gly Lys Thr Asn Gln Val Met Ser Ser Met Lys Gln Met Glu Glu Arg Leu Gln His Ser Glu Arg Ala Arg Gln Gly Ala Glu Glu Arg Ser His Lys Leu Gln Glu Leu Gly Gly Arg Ile Gly Ala Leu Gln Leu Gln Leu Ser Gln Leu His Glu Gln Cys Ser Ser Leu Glu Lys Glu Leu Lys Ser Glu Lys Glu Gln Arg Gln Ala Leu Gln Arg Glu Leu Gln His Glu Lys Asp Thr Ser Ser Leu Leu Arg Met Glu Leu Gln Gln Val Glu Gly Leu Lys Lys Glu Leu Arg Glu Leu Gln Asp Glu Lys 

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Ala Glu Leu Gln Lys Ile Cys Glu Glu Gln Glu Gln Ala Leu Gln Glu
Met Gly Leu His Leu Ser Gln Ser Lys Leu Lys Met Glu Asp Ile Lys
                        615
                                            620
Glu Val Asn Gln Ala Leu Lys Gly His Ala Trp Leu Lys Asp Asp Glu
                   630
                                        635
Ala Thr His Cys Arg Gln Cys Glu Lys Glu Phe Ser Ile Ser Arg Arg
               645
                                  650
Lys His His Cys Arg Asn Cys Gly His Ile Phe Cys Asn Thr Cys Ser
            660
                                665
Ser Asn Glu Leu Ala Leu Pro Ser Tyr Pro Lys Pro Val Arg Val Cys
                            680
Asp Ser Cys His Thr Leu Leu Gln Arg Cys Ser Ser Thr Ala Ser
                        695
                                            700
      <210> 192
      <211> 331
      <212> PRT
      <213> Homo sapien
      <400> 192
Arg Ala Gly Ala Ser Ala Met Ala Leu Arg Lys Glu Leu Leu Lys Ser
                 5
                                    10
Ile Trp Tyr Ala Phe Thr Ala Leu Asp Val Glu Lys Ser Gly Lys Val
                               25
Ser Lys Ser Gln Leu Lys Val Leu Ser His Asn Leu Tyr Thr Val Leu
                            40
His Ile Pro His Asp Pro Val Ala Leu Glu Glu His Phe Arg Asp Asp
Asp Asp Gly Pro Val Ser Ser Gln Gly Tyr Met Pro Tyr Leu Asn Lys
                    70
                                        75
Tyr Ile Leu Asp Lys Val Glu Glu Gly Ala Phe Val Lys Glu His Phe
               85
Asp Glu Leu Cys Trp Thr Leu Thr Ala Lys Lys Asn Tyr Arg Ala Asp
                               105
Ser Asn Gly Asn Ser Met Leu Ser Asn Gln Asp Ala Phe Arg Leu Trp
                            120
                                               125
Cys Leu Phe Asn Phe Leu Ser Glu Asp Lys Tyr Pro Leu Ile Met Val
                       135
                                           140
Pro Asp Glu Val Glu Tyr Leu Leu Lys Lys Val Leu Ser Ser Met Ser
                   150
                                        155
Leu Glu Val Ser Leu Gly Glu Leu Glu Glu Leu Leu Ala Gln Glu Ala
                165
                                    170
Gln Val Ala Gln Thr Thr Gly Gly Leu Ser Val Trp Gln Phe Leu Glu
                                185
Leu Phe Asn Ser Gly Arg Cys Leu Arg Gly Val Gly Arg Asp Thr Leu
                           200
Ser Met Ala Ile His Glu Val Tyr Gln Glu Leu Ile Gln Asp Val Leu
                       215
                                           220
Lys Gln Gly Tyr Leu Trp Lys Arg Gly His Leu Arg Arg Asn Trp Ala
                   230
                                       235
Glu Arg Trp Phe Gln Leu Gln Pro Ser Cys Leu Cys Tyr Phe Gly Ser
               245
                                    250
Glu Glu Cys Lys Glu Lys Arg Gly Ile Ile Pro Leu Asp Ala His Cys
```

```
260
                               265
Cys Val Glu Val Leu Pro Asp Arg Asp Gly Lys Arg Cys Met Phe Cys
                           280
                                   285
Val Lys Thr Ala Thr Arg Thr Tyr Glu Met Ser Ala Ser Asp Thr Arg
                      295
Gln Arg Gln Glu Trp Thr Ala Ala Ile Gln Met Ala Ile Arg Leu Gln
                   310
                                      315
Ala Glu Gly Lys Thr Ser Leu His Lys Asp Leu
            325
      <210> 193
      <211> 475
      <212> PRT
      <213> Homo sapien
      <400> 193
Lys Asn Ser Pro Leu Leu Ser Val Ser Ser Gln Thr Ile Thr Lys Glu
                       10
Asn Asn Arg Asn Val His Leu Glu His Ser Glu Gln Asn Pro Gly Ser
                               25
Ser Ala Gly Asp Thr Ser Ala Ala His Gln Val Val Leu Gly Glu Asn
                           40
Leu Ile Ala Thr Ala Leu Cys Leu Ser Gly Ser Gly Ser Gln Ser Asp
                       55
                                           60
Leu Lys Asp Val Ala Ser Thr Ala Gly Glu Glu Gly Asp Thr Ser Leu
                   70
Arg Glu Ser Leu His Pro Val Thr Arg Ser Leu Lys Ala Gly Cys His
               85
                                   90
Thr Lys Gln Leu Ala Ser Arg Asn Cys Ser Glu Glu Lys Ser Pro Gln
                              105
Thr Ser Ile Leu Lys Glu Gly Asn Arg Asp Thr Ser Leu Asp Phe Arg
                          120
Pro Val Val Ser Pro Ala Asn Gly Val Glu Gly Val Arg Val Asp Gln
                      135
                                         140
Asp Asp Asp Gln Asp Ser Ser Leu Lys Leu Ser Gln Asn Ile Ala
                   150
                                      155
Val Gln Thr Asp Phe Lys Thr Ala Asp Ser Glu Val Asn Thr Asp Gln
               165
                                  170
Asp Ile Glu Lys Asn Leu Asp Lys Met Met Thr Glu Arg Thr Leu Leu
           180
                              185
Lys Glu Arg Tyr Gln Glu Val Leu Asp Lys Gln Arg Gln Val Glu Asn
                           200
Gln Leu Gln Val Gln Leu Lys Gln Leu Gln Gln Arg Arg Glu Glu
                       215
                                          220
Met Lys Asn His Gln Glu Ile Leu Lys Ala Ile Gln Asp Val Thr Ile
                   230
                                      235
Lys Arg Glu Glu Thr Lys Lys Ile Glu Lys Glu Lys Glu Phe
                                  250
Leu Gln Lys Glu Gln Asp Leu Lys Ala Glu Ile Glu Lys Leu Cys Glu
           260
                              265
Lys Gly Arg Arg Glu Val Trp Glu Met Glu Leu Asp Arg Leu Lys Asn
                          280
                                              285
Gln Asp Gly Glu Ile Asn Arg Asn Ile Met Glu Glu Thr Glu Arg Ala
```

```
Trp Lys Ala Glu Ile Leu Ser Leu Glu Ser Arg Lys Glu Leu Leu Val
                   310
                                      315
Leu Lys Leu Glu Glu Ala Glu Lys Glu Ala Glu Leu His Leu Thr Tyr
               325
                                 330
Leu Lys Ser Thr Pro Pro Thr Leu Glu Thr Val Arg Ser Lys Gln Glu
          340
                             345
Trp Glu Thr Arg Leu Asn Gly Val Arg Ile Met Lys Lys Asn Val Arg
                         360
                                  365
Asp Gln Phe Asn Ser His Ile Gln Leu Val Arg Asn Gly Ala Lys Leu
                      375
                                        380
Ser Ser Leu Pro Gln Ile Pro Thr Pro Thr Leu Pro Pro Pro Ser
                  390 395
Glu Thr Asp Phe Met Leu Gln Val Phe Gln Pro Ser Pro Ser Leu Ala
               405
                                  410
Pro Arg Met Pro Phe Ser Ile Gly Gln Val Thr Met Pro Met Val Met
                              425
Pro Ser Ala Asp Pro Arg Ser Leu Ser Phe Pro Ile Leu Asn Pro Ala
       435
                          440
Leu Ser Gln Pro Ser Gln Pro Ser Ser Pro Leu Pro Gly Ser His Gly
                      455 460
Arg Asn Ser Pro Gly Leu Gly Ser Leu Val Ser
                  470
     <210> 194
     <211> 241
     <212> PRT
     <213> Homo sapien
     <400> 194
Met Ser Gly Glu Ser Ala Arg Ser Leu Gly Lys Gly Ser Ala Pro Pro
        5
                                 10
Gly Pro Val Pro Glu Gly Ser Ile Arg Ile Tyr Ser Met Arg Phe Cys
Pro Phe Ala Glu Arg Thr Arg Leu Val Leu Lys Ala Lys Gly Ile Arg
                          40
His Glu Val Ile Asn Ile Asn Leu Lys Asn Lys Pro Glu Trp Phe Phe
                      55
                                        60
Lys Lys Asn Pro Phe Gly Leu Val Pro Val Leu Glu Asn Ser Gln Gly
                  70
                                     75
Gln Leu Ile Tyr Glu Ser Ala Ile Thr Cys Glu Tyr Leu Asp Glu Ala
              85
                                 90
Tyr Pro Gly Lys Lys Leu Leu Pro Asp Asp Pro Tyr Glu Lys Ala Cys
           100
                             105
Gln Lys Met Ile Leu Glu Leu Phe Ser Lys Val Pro Ser Leu Val Gly
                          120
                                             125
Ser Phe Ile Arg Ser Gln Asn Lys Glu Asp Tyr Ala Gly Leu Lys Glu
                      135
Glu Phe Arg Lys Glu Phe Thr Lys Leu Glu Glu Val Leu Thr Asn Lys
                 150
                                    155
Lys Thr Thr Phe Phe Gly Gly Asn Ser Ile Ser Met Ile Asp Tyr Leu
              165
                                170 175
Ile Trp Pro Trp Phe Glu Arg Leu Glu Ala Met Lys Leu Asn Glu Cys
           180
                  185
```

Val Asp His Thr Pro Lys Leu Lys Leu Trp Met Ala Ala Met Lys Glu

```
200
                                                205
Asp Pro Thr Val Ser Ala Leu Leu Thr Ser Glu Lys Asp Trp Gln Gly
             215
                                        220
Phe Leu Glu Leu Tyr Leu Gln Asn Ser Pro Glu Ala Cys Asp Tyr Gly
Leu
      <210> 195
      <211> 138
      <212> PRT
      <213> Homo sapien
      <400> 195
Gln Thr Lys Ile Leu Glu Glu Asp Leu Glu Gln Ile Lys Leu Ser Leu
                                    10
Arg Glu Arg Gly Arg Glu Leu Thr Thr Gln Arg Gln Leu Met Gln Glu
Arg Ala Glu Glu Gly Lys Gly Pro Ser Lys Ala Gln Arg Gly Ser Leu
                            40
Glu His Met Lys Leu Ile Leu Arg Asp Lys Glu Lys Glu Val Glu Cys
                        55
Gln Gln Glu His Ile His Glu Leu Gln Glu Leu Lys Asp Gln Leu Glu
                    70
                                        75
Gln Gln Leu Gln Gly Leu His Arg Lys Val Gly Glu Thr Ser Leu Leu
               85
Leu Ser Gln Arg Glu Gln Glu Ile Val Val Leu Gln Gln Gln Leu Gln
                                105
Glu Ala Arg Glu Gln Gly Glu Leu Lys Glu Gln Ser Leu Gln Ser Gln
                            120
Leu Asp Glu Ala Gln Arg Ala Leu Ala Gln
    130
                        135
      <210> 196
      <211> 102
      <212> PRT
      <213> Homo sapien
      <400> 196
Met Ser Lys Arg Lys Ala Pro Gln Glu Thr Leu Asn Gly Gly Ile Thr
                                    10
Asp Met Leu Thr Glu Leu Ala Asn Phe Glu Lys Asn Val Ser Gln Ala
Ile His Lys Tyr Asn Ala Tyr Arg Lys Ala Ala Ser Val Ile Ala Lys
Tyr Pro His Lys Ile Lys Ser Gly Ala Glu Ala Lys Lys Leu Pro Gly
                       55
Val Gly Thr Lys Ile Ala Glu Lys Ile Asp Glu Phe Leu Ala Thr Gly
                                       75
Lys Leu Arg Lys Leu Glu Lys Ile Arg Gln Asp Asp Thr Ser Ser Ser
Ile Asn Phe Leu Thr Arg
           100
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<210> 197
       <211> 138
       <212> PRT
      <213> Homo sapien
      <400> 197
Glu Ala Asn Glu Val Thr Asp Ser Ala Tyr Met Gly Ser Glu Ser Thr
Tyr Ser Glu Cys Glu Thr Phe Thr Asp Glu Asp Thr Ser Thr Leu Val
                                25
His Pro Glu Leu Gln Pro Glu Gly Asp Ala Asp Ser Ala Gly Gly Ser
Ala Val Pro Ser Glu Cys Leu Asp Ala Met Glu Glu Pro Asp His Gly
Ala Leu Leu Leu Pro Gly Arg Pro His Pro His Gly Gln Ser Val
                                         75
Ile Thr Val Ile Gly Gly Glu Glu His Phe Glu Asp Tyr Gly Glu Gly
Ser Glu Ala Glu Leu Ser Pro Glu Thr Leu Cys Asn Gly Gln Leu Gly
                                105
Cys Ser Asp Pro Ala Phe Leu Thr Pro Ser Pro Thr Lys Arg Leu Ser
                            120
Ser Lys Lys Val Ala Arg Tyr Leu His Gln
    130
                        135
      <210> 198
      <211> 100
      <212> PRT
      <213> Homo sapien
      <400> 198
Met Gly Asp Val Lys Asn Phe Leu Tyr Ala Trp Cys Gly Lys Arg Lys
                                    10
Met Thr Pro Ser Tyr Glu Ile Arg Ala Val Gly Asn Lys Asn Arg Gln
                                25
Lys Phe Met Cys Glu Val Gln Val Glu Gly Tyr Asn Tyr Thr Gly Met
                            40
Gly Asn Ser Thr Asn Lys Lys Asp Ala Gln Ser Asn Ala Ala Arg Asp
                        55
Phe Val Asn Tyr Leu Val Arg Ile Asn Glu Ile Lys Ser Glu Glu Val
                                        75
Pro Ala Phe Gly Val Ala Ser Pro Pro Pro Leu Thr Asp Thr Pro Asp
                                    90
Thr Thr Ala Asn
            100
      <210> 199
      <211> 127
      <212> PRT
      <213> Homo sapien
     <400> 199
Met Val Lys Glu Thr Thr Tyr Tyr Asp Val Leu Gly Val Lys Pro Asn
                                    10
```

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Ala Thr Gln Glu Leu Lys Lys Ala Tyr Arg Lys Leu Ala Leu Lys
Tyr His Pro Asp Lys Asn Pro Asn Glu Gly Glu Lys Phe Lys Gln Ile
                            40
Ser Gln Ala Tyr Glu Val Leu Ser Asp Ala Lys Lys Arg Glu Leu Tyr
                        55
Asp Lys Gly Gly Glu Gln Ala Ile Lys Glu Gly Gly Ala Gly Gly Gly
                                        75
Phe Gly Ser Pro Met Asp Ile Phe Asp Met Phe Phe Gly Gly Gly Gly
               8.5
                                   90
Arg Met Gln Arg Glu Arg Arg Gly Lys Asn Val Val His Gln Leu Ser
                                105
Val Thr Leu Glu Asp Leu Tyr Asn Gly Ala Thr Arg Lys Leu Ala
                            120
      <210> 200
      <211> 90
      <212> PRT
      <213> Homo sapien
      <400> 200
Met Ala Cys Pro Leu Asp Gln Ala Ile Gly Leu Leu Val Ala Ile Phe
                                    10
His Lys Tyr Ser Gly Arg Glu Gly Asp Lys His Thr Leu Ser Lys Lys
                                25
Glu Leu Lys Glu Leu Ile Gln Lys Glu Leu Thr Ile Gly Ser Lys Leu
        35
                            40
Gln Asp Ala Glu Ile Ala Arg Leu Met Glu Asp Leu Asp Arg Asn Lys
                        55
Asp Gln Glu Val Asn Phe Gln Glu Tyr Val Thr Phe Leu Gly Ala Leu
                    70
Ala Leu Ile Tyr Asn Glu Ala Leu Lys Gly
      <210> 201
      <211> 120
      <212> PRT
      <213> Homo sapien
      <400> 201
Met Glu Thr Pro Ser Gln Arg Arg Ala Thr Arg Ser Gly Ala Gln Ala
1
                5
Ser Ser Thr Pro Leu Ser Pro Thr Arg Ile Thr Arg Leu Gln Glu Lys
                                25
Glu Asp Leu Gln Glu Leu Asn Asp Arg Leu Ala Val Tyr Ile Asp Arg
Val Arg Ser Leu Glu Thr Glu Asn Ala Gly Leu Arg Leu Arg Ile Thr
                        55
Glu Ser Glu Glu Val Val Ser Arg Glu Val Ser Gly Ile Lys Ala Ala
                    70
                                        75
Tyr Glu Ala Glu Leu Gly Asp Ala Arg Lys Thr Leu Asp Ser Val Ala
                                    90
Lys Glu Arg Ala Arg Leu Gln Leu Glu Leu Ser Lys Val Arg Glu Glu
```

```
Phe Lys Glu Leu Lys Ala Arg Asn
        115
      <210> 202
      <211> 177
      <212> PRT
      <213> Homo sapien
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Met Ala Ala Gly Val Glu Ala Ala Glu Val Ala Ala Thr Glu Ile
                                    1.0
Lys Met Glu Glu Glu Ser Gly Ala Pro Gly Val Pro Ser Gly Asn Gly
            20
                                25
Ala Pro Gly Pro Lys Gly Glu Gly Glu Arg Pro Ala Gln Asn Glu Lys
Arg Lys Glu Lys Asn Ile Lys Arg Gly Gly Asn Arg Phe Glu Pro Tyr
                        55
Ala Asn Pro Thr Lys Arg Tyr Arg Ala Phe Ile Thr Asn Ile Pro Phe
                   70
                                       75
Asp Val Lys Trp Gln Ser Leu Lys Asp Leu Val Lys Glu Lys Val Gly
               8.5
                                   90
Glu Val Thr Tyr Val Glu Leu Leu Met Asp Ala Glu Gly Lys Ser Arg
           100
                               105
Gly Cys Ala Val Val Glu Phe Lys Met Glu Glu Ser Met Lys Lys Ala
       115
              120
Ala Glu Val Leu Asn Lys His Ser Leu Ser Gly Arg Pro Leu Lys Val
                       135
Lys Glu Asp Pro Asp Gly Glu His Ala Arg Arg Ala Met Gln Lys Ala
                    150
                                       155
Gly Arg Leu Gly Ser Thr Val Phe Val Ala Asn Leu Asp Tyr Lys Val
                                    170
Gly
      <210> 203
      <211> 164
      <212> PRT
      <213> Homo sapien
      <400> 203
Met Arg Leu Ala Val Gly Ala Leu Leu Val Cys Ala Val Leu Gly Leu
                 5
Cys Leu Ala Val Pro Asp Lys Thr Val Arg Trp Cys Ala Val Ser Glu
His Glu Ala Thr Lys Cys Gln Ser Phe Arg Asp His Met Lys Ser Val
                            40
Ile Pro Ser Asp Gly Pro Ser Val Ala Cys Val Lys Lys Ala Ser Tyr
Leu Asp Cys Ile Arg Ala Ile Ala Ala Asn Glu Ala Asp Ala Val Thr
                   70
                                       75
Leu Asp Ala Gly Leu Val Tyr Asp Ala Tyr Leu Ala Pro Asn Asn Leu
                                   90
Lys Pro Val Val Ala Glu Phe Tyr Gly Ser Lys Glu Asp Pro Gln Thr
```

```
        Phe
        Tyr
        Tyr
        Ala
        Val
        Val
        Lys
        Lys</th
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<210> 204 <211> 241 <212> PRT

<213> Homo sapien

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Phe Leu Glu Leu Tyr Leu Gln Asn Ser Pro Glu Ala Cys Asp Tyr Gly

235

<210> 205 <211> 160

225

Leu

<212> PRT

<213> Homo sapien

230

<400> 205

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Met Gln Ile Phe Val Lys Thr Leu Thr Gly Lys Thr Ile Thr Leu Glu
Val Glu Pro Ser Asp Thr Ile Glu Asn Val Lys Ala Lys Ile Gln Asp
                               25
Lys Glu Gly Ile Pro Pro Asp Gln Gln Arg Leu Ile Phe Ala Gly Lys
                           40
Gln Leu Glu Asp Gly Arg Thr Leu Ser Asp Tyr Asn Ile Gln Lys Glu
                       55
Ser Thr Leu His Leu Val Leu Arg Leu Arg Gly Gly Met Gln Ile Phe
                   70
                                        75
Val Lys Thr Leu Thr Gly Lys Thr Ile Thr Leu Glu Val Glu Pro Ser
                                   90
Asp Thr Ile Glu Asn Val Lys Ala Lys Ile Gln Asp Lys Glu Gly Ile
                                105
Pro Pro Asp Gln Gln Arg Leu Ile Phe Ala Gly Lys Gln Leu Glu Asp
        115
                            120
Gly Arg Thr Leu Ser Asp Tyr Asn Ile Gln Lys Glu Ser Thr Leu His
                      135
                                           140
Leu Val Leu Arg Leu Arg Gly Gly Met Gln Ile Phe Val Lys Thr Leu
                   150
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      <211> 197
      <212> PRT
      <213> Homo sapien
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Thr Ser Pro Ser Glu Ala Cys Ala Pro Leu Leu Ile Ser Leu Ser Thr
Leu Ile Tyr Asn Gly Ala Leu Pro Cys Gln Cys Asn Pro Gln Gly Ser
                                25
Leu Ser Ser Glu Cys Asn Pro His Gly Gly Gln Cys Leu Cys Lys Pro
Gly Val Val Gly Arg Arg Cys Asp Leu Cys Ala Pro Gly Tyr Tyr Gly
Phe Gly Pro Thr Gly Cys Gln Gly Ala Cys Leu Gly Cys Arg Asp His
Thr Gly Gly Glu His Cys Glu Arg Cys Ile Ala Gly Phe His Gly Asp
               85
                                    90
Pro Arg Leu Pro Tyr Gly Gly Gln Cys Arg Pro Cys Pro Cys Pro Glu
                                105
Gly Pro Gly Ser Gln Arg His Phe Ala Thr Ser Cys His Gln Asp Glu
                            120
Tyr Ser Gln Gln Ile Val Cys His Cys Arg Ala Gly Tyr Thr Gly Leu
                        135
                                            140
Arg Cys Glu Ala Cys Ala Pro Gly His Phe Gly Asp Pro Ser Arg Pro
                   150
                                       155
Gly Gly Arg Cys Gln Leu Cys Glu Cys Ser Gly Asn Ile Asp Pro Met
               165
                                   170
Asp Pro Asp Ala Cys Asp Pro His Thr Gly Gln Cys Leu Arg Cys Leu
                               185
           180
His His Thr Glu Gly
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<210> 207
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      <212> PRT
      <213> Homo sapien
     <400> 207
Ile Ile Arg Gln Gln Gly Leu Ala Ser Tyr Asp Tyr Val Arg Arg Arg
                                    10
Leu Thr Ala Glu Asp Leu Phe Glu Ala Arg Ile Ile Ser Leu Glu Thr
                               2.5
Tyr Asn Leu Leu Arg Glu Gly Thr Arg Ser Leu Arg Glu Ala Leu Glu
Ala Glu Ser Ala Trp Cys Tyr Leu Tyr Gly Thr Gly Ser Val Ala Gly
                        55
Val Tyr Leu Pro Gly Ser Arg Gln Thr Leu Ser Ile Tyr Gln Ala Leu
                                       75
Lys Lys Gly Leu Leu Ser Ala Glu Val Ala Arg Leu Leu Glu Ala
Gln Ala Ala Thr Gly Phe Leu Leu Asp Pro Val Lys Gly Glu Arg Leu
          100
                               105
Thr Val Asp Glu Ala Val Arg Lys Gly Leu Val Gly Pro Glu Leu His
                           120
                                               125
      115
Asp Arg Leu Leu Ser Ala Glu Arg Ala Val Thr Gly Tyr Arg Asp Pro
                       135
                                           140
Tyr Thr Glu Gln Thr Ile Ser Leu Phe Gln Ala Met Lys Lys Glu Leu
                   150
                                       155
Ile Pro Thr Glu Glu Ala Leu Arg Leu Trp Met Pro Ser Trp Pro
                165
                                    170
      <210> 208
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      <213> Homo sapien
     <400> 208
Met Ala Ala Gly Val Glu Ala Ala Ala Glu Val Ala Ala Thr Glu Ile
                                    1.0
Lys Met Glu Glu Ser Gly Ala Pro Gly Val Pro Ser Gly Asn Gly
                                25
Ala Pro Gly Pro Lys Gly Glu Gly Glu Arg Pro Ala Gln Asn Glu Lys
                            40
Arg Lys Glu Lys Asn Ile Lys Arg Gly Gly Asn Arg Phe Glu Pro Tyr
Ala Asn Pro Thr Lys Arg Tyr Arg Ala Phe Ile Thr Asn Ile Pro Phe
                                       75
                   70
Asp Val Lys Trp Gln Ser Leu Lys Asp Leu Val Lys Glu Lys Val Gly
                                   90
Glu Val Thr Tyr Val Glu Leu Leu Met Asp Ala Glu Gly Lys Ser Arg
           100
                               105
Gly Cys Ala Val Val Glu Phe Lys Met Glu Glu Ser Met Lys Lys Ala
                           120
       115
```

Ala Glu Val Leu Asn Lys His Ser Leu Ser Gly Arg Pro Leu Lys Val

Lys Glu Asp Pro Asp Gly Glu His Ala Arg Arg Ala Met Gln Lys Val

140

```
155
                 150
Met Ala Thr Thr Gly Gly Met Gly Met Gly Pro Gly Pro Gly Met
               165
                                 170
Ile
     <210> 209
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Asp Leu Gln Asp Met Phe Ile Val His Thr Ile Glu Glu Ile Glu Gly
                                 10
              5
Leu Ile Ser Ala His Asp Gln Phe Lys Ser Thr Leu Pro Asp Ala Asp
                              25
Arg Glu Arg Glu Ala Ile Leu Ala Ile His Lys Glu Ala Gln Arg Ile
                         40
Ala Glu Ser Asn His Ile Lys Leu Ser Gly Ser Asn Pro Tyr Thr Thr
                     55
Val Thr Pro Gln Ile Ile Asn Ser Lys Trp Glu Lys Val Gln Gln Leu
    70
                                    75
Val Pro Lys Arg Asp His Ala Leu Leu Glu Glu Gln Ser Lys Gln Gln
                                90
             85
Ser Asn Glu His Leu Arg Arg Gln Phe Ala Ser Gln Ala Asn Val Val
                             105
Gly Pro Trp Ile Gln Thr Lys Met Glu Glu Ile Gly Arg Ile Ser Ile
       115
                         120
Glu Met Asn Gly Thr Leu Glu Asp Gln Leu Ser His Leu Lys Gln Tyr
                      135
Glu Arg Ser Ile Val Asp Tyr Lys Pro Asn Leu Asp Leu Leu Glu Gln
                 150
                                    155
Gln His Gln Leu Ile Gln Glu Ala Leu Ile Phe Asp Asn Lys His Thr
              165
                                170 175
Asn Tyr Thr Met Glu His Ile Arg Val Gly Trp Glu Gln Leu Leu Thr
                            185
          180
Thr Ile Ala Arg
       195
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     <211> 156
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     <213> Homo sapien
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Lys Leu Thr Ile Glu Ser Thr Pro Phe Asn Val Ala Glu Gly Lys Glu
                                10
Val Leu Leu Leu Ala His Asn Leu Pro Gln Asn Arg Ile Gly Tyr Ser
                             25
Trp Tyr Lys Gly Glu Arg Val Asp Gly Asn Ser Leu Ile Val Gly Tyr
                         40
Val Ile Gly Thr Gln Gln Ala Thr Pro Gly Pro Ala Tyr Ser Gly Arg
                      55
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Glu Thr Ile Tyr Pro Asn Ala Ser Leu Leu Ile Gln Asn Val Thr Gln

```
70
65
Asn Asp Thr Gly Phe Tyr Thr Leu Gln Val Ile Lys Ser Asp Leu Val
                                 90
              85
Asn Glu Glu Ala Thr Gly Gln Phe His Val Tyr Pro Glu Leu Pro Lys
                             105
Pro Ser Ile Ser Ser Asn Asn Ser Asn Pro Val Glu Asp Lys Asp Ala
       115 120
Val Ala Phe Thr Cys Glu Pro Glu Val Gln Asn Thr Thr Tyr Leu Trp
        135
Trp Val Asn Gly Gln Ser Leu Pro Val Ser Pro Lys
                 150
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Met Glu Ser Pro Ser Ala Pro Pro His Arg Trp Cys Ile Pro Trp Gln
                                 10
Arg Leu Leu Thr Ala Ser Leu Leu Thr Phe Trp Asn Pro Pro Thr
   20
                             25
Thr Ala Lys Leu Thr Ile Glu Ser Thr Pro Phe Asn Val Ala Glu Gly
                                             45
                         40
Lys Glu Val Leu Leu Val His Asn Leu Pro Gln His Leu Phe Gly
                      55
Tyr Ser Trp Tyr Lys Gly Glu Arg Val Asp Gly Asn Arg Gln Ile Ile
                   70
Gly Tyr Val Ile Gly Thr Gln Gln Ala Thr Pro Gly
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     <211> 142
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Glu Lys Gln Lys Asn Lys Glu Phe Ser Gln Thr Leu Glu Asn Glu Lys
                                 10
Asn Thr Leu Leu Ser Gln Ile Ser Thr Lys Asp Gly Glu Leu Lys Met
                              25
Leu Gln Glu Glu Val Thr Lys Met Asn Leu Leu Asn Gln Gln Ile Gln
Glu Glu Leu Ser Arg Val Thr Lys Leu Lys Glu Thr Ala Glu Glu
                      55
Lys Asp Asp Leu Glu Glu Arg Leu Met Asn Gln Leu Ala Glu Leu Asn
                                     75
Gly Ser Ile Gly Asn Tyr Cys Gln Asp Val Thr Asp Ala Gln Ile Lys
                                 90
Asn Glu Leu Leu Glu Ser Glu Met Lys Asn Leu Lys Lys Cys Val Ser
                              105
Glu Leu Glu Glu Lys Gln Gln Leu Val Lys Glu Lys Thr Lys Val
       115 120
Glu Ser Glu Ile Arg Lys Glu Tyr Leu Glu Lys Ile Gln Gly
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<211> 148

130 135 140 <210> 213 <211> 142 <212> PRT <213> Homo sapien <400> 213 Gly Gly Tyr Gly Gly Tyr Gly Gly Val Leu Thr Ala Ser Asp Gly 10 Leu Leu Ala Gly Asn Glu Lys Leu Thr Met Gln Asn Leu Asn Asp Arg 20 Leu Ala Ser Tyr Leu Asp Lys Val Arg Ala Leu Glu Ala Ala Asn Gly Glu Leu Glu Val Lys Ile Arg Asp Trp Tyr Gln Lys Gln Gly Pro Gly 55 Pro Ser Arg Asp Tyr Ser His Tyr Tyr Thr Thr Ile Gln Asp Leu Arg 75 Asp Lys Ile Leu Gly Ala Thr Ile Glu Asn Ser Arg Ile Val Leu Gln 85 Ile Asp Asn Ala Arg Leu Ala Ala Asp Asp Phe Arg Thr Lys Phe Glu 100 105 Thr Glu Gln Ala Leu Arg Met Ser Val Glu Ala Asp Ile Asn Gly Leu 120 125 Arg Arg Val Leu Asp Glu Leu Thr Leu Ala Arg Thr Asp Leu 135 <210> 214 <211> 129 <212> PRT <213> Homo sapien <400> 214 Val Met Arg Val Asp Phe Asn Val Pro Met Lys Asn Asn Gln Ile Thr 10 Asn Asn Gln Arg Ile Lys Ala Ala Val Pro Ser Ile Lys Phe Cys Leu 25 Asp Asn Gly Ala Lys Ser Val Val Leu Met Ser His Leu Gly Arg Pro 40 Asp Gly Val Pro Met Pro Asp Lys Tyr Ser Leu Glu Pro Val Ala Val 55 Glu Leu Arg Ser Leu Leu Gly Lys Asp Val Leu Phe Leu Lys Asp Cys 70 Val Gly Pro Glu Val Glu Lys Ala Cys Ala Asn Pro Ala Ala Gly Ser 90 Val Ile Leu Leu Glu Asn Leu Arg Phe His Val Glu Glu Glu Lys 105 Gly Lys Asp Ala Ser Gly Asn Lys Val Lys Ala Glu Pro Ala Lys Ile 120 Glu <210> 215

<212> PRT <213> Homo sapien <400> 215 Met Ala Thr Leu Lys Glu Lys Leu Ile Ala Pro Val Ala Glu Glu 10 Ala Thr Val Pro Asn Asn Lys Ile Thr Val Val Gly Val Gly Gln Val 20 25 Gly Met Ala Cys Ala Ile Ser Ile Leu Gly Lys Ser Leu Ala Asp Glu 4.0 Leu Ala Leu Val Asp Val Leu Glu Asp Lys Leu Lys Gly Glu Met Met 55 Asp Leu Gln His Gly Ser Leu Phe Leu Gln Thr Pro Lys Ile Val Ala 70 Asp Lys Asp Tyr Ser Val Thr Ala Asn Ser Lys Ile Val Val Thr 90 85 Ala Gly Val Arg Gln Gln Glu Gly Glu Ser Arg Leu Asn Leu Val Gln 105 Arg Asn Val Asn Val Phe Lys Phe Ile Ile Pro Gln Ile Val Lys Tyr 120 Ser Pro Asp Cys Ile Ile Ile Val Val Ser Asn Pro Val Asp Ile Leu 135 130 Thr Tyr Val Thr 145 <210> 216 <211> 527 <212> PRT <213> Homo sapien <400> 216 Gln Arg Ala Pro Gly Ile Glu Glu Lys Ala Ala Glu Asn Gly Ala Leu 10 Gly Ser Pro Glu Arg Glu Glu Lys Val Leu Glu Asn Gly Glu Leu Thr 25 Pro Pro Arg Arg Glu Glu Lys Ala Leu Glu Asn Gly Glu Leu Arg Ser 40 Pro Glu Ala Gly Glu Lys Val Leu Val Asn Gly Gly Leu Thr Pro Pro 55 60 Lys Ser Glu Asp Lys Val Ser Glu Asn Gly Gly Leu Arg Phe Pro Arg 70 75 Asn Thr Glu Arg Pro Pro Glu Thr Gly Pro Trp Arg Ala Pro Gly Pro 90 Trp Glu Lys Thr Pro Glu Ser Trp Gly Pro Ala Pro Thr Ile Gly Glu 105 100 Pro Ala Pro Glu Thr Ser Leu Glu Arg Ala Pro Ala Pro Ser Ala Val 120 125 Val Ser Ser Arg Asn Gly Gly Glu Thr Ala Pro Gly Pro Leu Gly Pro 135 140 Ala Pro Lys Asn Gly Thr Leu Glu Pro Gly Thr Glu Arg Arg Ala Pro 155 150 Glu Thr Gly Gly Ala Pro Arg Ala Pro Gly Ala Gly Arg Leu Asp Leu 165 170 175

Gly Ser Gly Gly Arg Ala Pro Val Gly Thr Gly Thr Ala Pro Gly Gly

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185
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Gly Pro Gly Ser Gly Val Asp Ala Lys Ala Gly Trp Val Asp Asn Thr
        195
                            200
Arg Pro Gln Pro Pro Pro Pro Leu Pro Pro Pro Pro Glu Ala Gln
                                           220
                       215
Pro Arg Arg Leu Glu Pro Ala Pro Pro Arg Ala Arg Pro Glu Val Ala
                                       235
                    230
Pro Glu Gly Glu Pro Gly Ala Pro Asp Ser Arg Ala Gly Gly Asp Thr
                                    250
               245
Ala Leu Ser Gly Asp Gly Asp Pro Pro Lys Pro Glu Arg Lys Gly Pro
                               265
                                                   270
            260
Glu Met Pro Arg Leu Phe Leu Asp Leu Gly Pro Pro Gln Gly Asn Ser
                            280
Glu Gln Ile Lys Ala Arg Leu Ser Arg Leu Ser Leu Ala Leu Pro Pro
                        295
                                            300
Leu Thr Leu Thr Pro Phe Pro Gly Pro Gly Pro Arg Arg Pro Pro Trp
                                        315
                    310
Glu Gly Ala Asp Ala Gly Ala Ala Gly Glu Ala Gly Gly Ala Gly
                                   330
Ala Pro Gly Pro Ala Glu Glu Asp Gly Glu Asp Glu Asp Glu Asp Glu
                               345
           340
Glu Glu Asp Glu Glu Ala Ala Pro Gly Ala Ala Ala Gly Pro Arg
                            360
                                               365
        355
Gly Pro Gly Arg Ala Arg Ala Ala Pro Val Pro Val Val Val Ser Ser
                       375
                                           380
Ala Asp Ala Asp Ala Arg Pro Leu Arg Gly Leu Leu Lys Ser Pro
                    390
                                        395
Arg Gly Ala Asp Glu Pro Glu Asp Ser Glu Leu Glu Arg Lys Arg Lys
                                    410
Met Val Ser Phe His Gly Asp Val Thr Val Tyr Leu Phe Asp Gln Glu
            420
                                425
                                                    430
Thr Pro Thr Asn Glu Leu Ser Val Gln Ala Pro Pro Glu Gly Asp Thr
                            440
Asp Pro Ser Thr Pro Pro Ala Pro Pro Thr Pro Pro His Pro Ala Thr
                        455
                                            460
Pro Gly Asp Gly Phe Pro Ser Asn Asp Ser Gly Phe Gly Gly Ser Phe
                                       475
                    470
Glu Trp Ala Glu Asp Phe Pro Leu Leu Pro Pro Pro Gly Pro Pro Leu
                                   490
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Cys Phe Ser Arg Phe Ser Val Ser Pro Ala Leu Glu Thr Pro Gly Pro
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qtqaqatcqa qaataacaqa aqcaqcggag cattctggaa atattactat gatggaaagg 42	
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(AOO) 010	
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tetadagege eggggeadee ageeggagae eegegegeg geoorgagge ageeg	80
acacaagcae tactecety tyggetatay tyaaastaay tagaaastaay	40
congregation address address and address a	00
caacococc coccocaca agragaagaa agragaagaa agragaagaa	60
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ataaagacct tctatcttgt a 38	ÖΙ
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coccagoada coacggogad addydactae arthuring amend y	40
caggaccaga ggcccccgg ggaagacoca coccacgaag coggaacgacgacgacgac	00
gegacaagaa acceeeag acgeeaaoac aassaassa assaassa assaassa	60
gragadeagg dadaceacco regacionege googlegood router arrange	20
ggoodagaa aagaagaaa agaaaaa agaaaa agaaaa agaaaa agaaaa agaaaaa aagaaa	80
geaceeeee aaceeegeg acegure and and a second acegure	40
adoccogage adactorado ografica esta esta esta esta esta esta esta est	00
	60
addeceder address and address bland by the control of the control	20
cegagaacta ceeaacaaaa gaccaactag caagaaagaa aanay .	80
- cacocagaco ocaacagoorg	40
addatetige tadagetada ataaggaata teetaataa taaaaaa aa aa aa aa aa aa aa aa a	00
ggaccaaca coagaaaaa rrjjrjrrrr rringrjr r	60
tattatgtaa tgcttatata ccatagagtt tttaatagaa gagaaatcca tttcctccga 102	
gggtcactat taacaatgta cttccttaaa tttagtttaa tgattgtaat gggtgctgca 108	
tttgcacatt gcattaagtt atgatgagac gaattgttgt taaaaattat agcaaaaaga 114	
aatgtaaact tggttaaaat cctttcactc tttgtattgt tttttttaag gtttttattc 120	
cttaaatgta aaatgactac ctaatttttt gatgtaaata cattaaattc aaagagaaaa 120	
aaaatcaaaa aaaaaaaaa aaaaaaactc gag 129	93
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VZION HOMO Bapion	

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taaaqtqacc qqaatqttaq aqatqcaatt tgcagagctg gggcaaggaa gggctccttg
                                                                       120
                                                                       180
tcactgtagt tactttcctt gcagtggcca aatgcccaat aagaaggaat acatgaccac
tgctgtgggg agtcagcagg tgcgtgatgc agctggccac actccatcca cggccatgac
                                                                       240
ataaaacaga caagaagtaa ggctggactg taacacctca aggcctgctc cagtgaccca
                                                                       300
                                                                       360
ctttcttcag agaggeteta ccacacaca aaccacette caaatttaca etcagateae
tacaccatgt ctcccaagtt aaaacatgta tccacctaga ctttaaatgt gctttgtaac
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                                                                       480
tgttgatggc actgtacaga gggccaaagt atttcccatc agatagcatt tttctgaacc
catgcctctt gggacgagat cacaggactt gacccatcat caaataggac caggtgacct
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<213> Homo sapiens
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<223> n=A, T, C or G
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<213> Homo sapiens
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<223> n=A,T,C or G
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<211> 514
<212> DNA
<213> Homo sapiens
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<210> 284
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<212> DNA
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<213> Homo sapiens
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<213> Homo sapiens
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<212> DNA
<213> Homo sapiens
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ccaacggcag gaaaaggagc tacttcagtc agcaacagag ggaccagcga cctgcagctt 720
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actattgaca gcttggagca gggcatttct agcctcatgg agcgcctgca tgttatggag 840
acgcagaaga aacaagaaag aaaggttcgg gtcaagtcac ccagaactca agtaggtagt 900
gaataccggg agtcctggcc ccctaactca aagttgcctc actcacagag ctctccaact 960
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gag
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tgagttaatg ggccgggacc gaaacctagc cccggacgag aagcgcagca acgtgcggtg 180
ggaccacgag agcgtttgta aatattatct ctgtggtttt tgtcctgcgg aattgttcac 240
aaatacacgt tctgatcttg gtccgtgtga aaaaattcat gatgaaaatc tacgaaaaca 300
gtatgagaag agctctcgtt tcatgaaagt tggctatgag agagattttt tgcgatactt 360
acagagetta ettgeagaag tagaaegtag gateagaega ggeeatgete gtttggeatt 420
atctcaaaac cagcagtctt ctggggccgc tggcccaaca ggcaaaaatg aagaaaaat 480
tcaggttcta acagacaaaa ttgatgtact tctgcaacag attgaagaat tagggtctga 540
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agaactgcta aggtccacaa cgtcgacaat tgaaagcttt gctgcacaag aaaaacaaat 660
ggaagtttgt gaagtatgtg gagccttttt aatagtagga gatgcccagt cccgggtaga 720
tgaccatttg atgggaaaac aacacatggg ctatgccaaa attaaagcta ctgtagaaga 780
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<210> 289
<211> 987
<212> DNA
<213> Homo sapiens
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catttggact tgggctgggg caggggctgg tgttgggcaa agctgggggt ccaggctgga 180
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gaagcagggg cccctccaga cgcagccttg ggagactcag catgtgcccc cctcccctca 240
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attaccagca totcagacaa gggcaggott caaacaggga ggcctgtggc aacccctccc 360
ctacgtctgg agctgagggg acagggggag ctgagaacaa agagaggaaa gaggagaaaa 420
geggegggg aacaggeggg gagegtgate ttettgeece catetteete aggggttggg 480
gggtacaaag tcggcggtgg cccatcccgc caggccccgc tgcccctcag aagaggccgc 540
agtectteag gttgttettg atgatgaeat eggtgaegge gteaaacaeg aactgeaegt 600
tcttggtgtc ggtggcgcac gtgaagtgcg tgtagatctc cttggtgtct ttgcgcttat 660
tcaggtcctc aaacttactc tggatgtagc tggctgcctc atcatatttg ttggcccctg 720
tatactcagg gaagcagatg gtcaggggac tgtgtgtgat cttctcctca aacaggtcct 780
tcttgttgag gaagaggatg atggacgtgt ctgtgaacca cttgttgttg cagatgctat 840
cgaatagett catgetetea tgeatgeggt teateteete gteeteaget ageaceaagt 900
cataggeget caaggetacg cagaagatga tggetgtgac geeetcaaag cagtggatee 960
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       <211> 300
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
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       \langle 223 \rangle n = A, T, C or G
       <400> 290
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                                                                          60
                                                                         120
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 acaagagcaa gctgattgca gggaagatca tcccaqccat tqccacgacc acagcaqccq
                                                                         180
                                                                         240
 tggttggcct tgtgtgtctg gagctgtaca aggttgtgca ggggcaccga cancttgact
 cctacangaa tgggtgcctc aacttgagcc ctgcctttct ttggtttctc tgaacccctt
                                                                         300
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       <211> 352
       <212> DNA
       <213> Homo sapien
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       <223> n = A, T, C or G
       <400> 291
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 cttctcaagg gtatttgcca tgtcccctga agagtttggc aagctggctc tgtggaagcg
                                                                         120
 gaatgagete aagaagaagg cetetetett etgatggeee ceacetgete egggaeggee
                                                                         180
                                                                         240
 cccttacccc tgctgcttca gggtttttcc ccggcgggtt gggaggggca ggaggtgggg
                                                                         300
 tggaaatngg qtgggcncct ttcctcaggt agagnggggg gccaaaacct ctgcngtccc
 cggagngage tatggaettt etteeceete acaaggntgg gggeeteetg et
                                                                         352
       <210> 292
       <211> 511
       <212> DNA
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<213> Homo sapien
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      <222> (1)...(511)
      <223> n = A, T, C or G
      <400> 292
                                                                         60
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ctatgccagg cgcatctcag ctaatccaaa agtaaatgag aaacttagaa aaagattgcc
aattccaaat caacatattt agagaaaatt ggaaaaggag aagcttacta cagctttatt
                                                                        180
                                                                        240
tgaggacttt ttaaagaacg ctgggttcta tctgtgagct gcaaatcttg gagcaaaaac
                                                                        300
cagagacatt gccagagcaa acaagaacag aaatacaaat ggagaactgg tcaaaagaca
taacccacag ttatcttgaa caagaaacta cggggataaa taaaagtacg canccagatg
                                                                        360
agcaactgac tatgaattct gagaaaagta tgcatcggaa atccactgaa ttagntaatg
                                                                        420
aaataacatg ngagaacaca gaatggccag gggcagagat caacgaattt tcanatcatc
                                                                        480
                                                                        511
agttcttatc cagatgatga gtctgtttac t
      <210> 293
      <211> 526
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(526)
      <223> n = A, T, C or G
      <400> 293
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acacggtacc accetgetet cetacttete aaacceacat ceaceaceca gacaggaggg
                                                                        120
tgcanacccc acaggaaatt acctcccgga gcactgactg atatttttcc ttaaaacaaa
                                                                        180
                                                                        240
aaaatggctg tctcagacta ataacagaac atcttaagag ctataccagc tattacagcc
tggtaatana agcagctttc taanaattcc caagtttata anaggcccaa naaatgcatt
                                                                        300
                                                                        360
tattctqttq tctattaagc ctccatgaca aggagaaagt tatgagtaaa tccttggttc
atcaggagtt aagagctgtg ngcctcatga ggagttaana gctgtgtgca taagcaggtt
                                                                        420
caaqaaacaa actcctgttt gtttgcctct ttgatggttc aaaaacattc agctgctttc
                                                                        480
                                                                        526
acctctanga caaaatgctt aaagaattta ctctcatcac cttggg
      <210> 294
      <211> 601
      <212> DNA
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      <220>
      <221> misc feature
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      \langle 223 \rangle n = A,T,C or G
      <400> 294
                                                                         60
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aggaaacatc aaaataaagt agatgaataa aaaggcacac tcgaaaaatt tgagcgcaga
aaggacagtt ctttttgttt tgtttctaat gtcggaagaa aaagaaagag atatattaaa
                                                                        180
atcattgttt tcaagtgaag gtttctgtca gttgaagtag ttagcaatgg cttctttct
                                                                        240
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300
cccqtqtcca aagcaggete tteetgeget gaettetgag gaggngttea gteetetgee
atgtataggc gatacatcaa ggcgacggcc actgcagaga tggcagggat cacccagttg
                                                                       360
                                                                       420
qtccaccaac tqqaactaga atcaatagta gtgataagag tttccggagg cttgtttaac
                                                                       480
tttggtctgt catctggatg gagctcccca atgatgaatg ttttggacat ttccctggca
                                                                       540
tetgtagant geeegacate eteaaagtte teagtageng teaecteeae ttgtteeett
aaaacttott coccaccagg atgotottoo agaaatttgg gncaaatcgn acaccttgtg
                                                                       600
                                                                       601
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      <211> 262
      <212> DNA
      <213> Homo sapien
      <400> 295
                                                                        60
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                                                                       120
caagggtgtt atgggcccag ctttgggggg ccagtcccga tgcactttga ggggtgttgg
                                                                       180
agaggggact occocactog cacttaacto aacggetete gggecetggg getgttttta
                                                                       240
ccatgtttgt ttttgaagct caggtgtctc acgtctgggc tgcaccaggc gaagagagaa
                                                                       262
attaaagatt tgaggttttt cc
      <210> 296
      <211> 598
      <212> DNA
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      <220>
      <221> misc_feature
      <222> (1)...(598)
      <223> n = A, T, C or G
      <400> 296
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tacatcaaac aggccaaaaa aaataaacag caacttcata gacaaaaaaag gaaaaaaaaa
gaaacctttt atctttggcc tttttaacca tctcatacaa accaactact tatagtacag
                                                                       180
                                                                       240
ctaaqtacat acacaaaaaa gttactggaa tgctcggaat aagattgttt ttctgttgtc
                                                                       300
attittgctt titttacaag gnttittitc tcctttgaga ttataatgaa catggncaca
                                                                       360
ccacaagtaa agtcagaagt aggacagana acgctccgaa ggctggtttg gtcatccgan
atcattaaaa atggctgacc ctaacaatat gtacaaaaat ataaaatgta aataaaaaat
                                                                       420
                                                                       480
acaaacaaat ttccttttta aagtactttt aagaaaaaaa gcagggcctt ggaagttttg
                                                                       540
qttctttttt cctcccctqt tqcaaattct catqqtttqg gttggqtggn gganancccg
                                                                       598
tqtcatctqc qggtggcact gccccggngg gcgggcgggc ctctctctcg aangngac
      <210> 297
      <211> 509
      <212> DNA
      <213> Homo sapien
      <400> 297
                                                                        60
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atcaacattg tcgtcattgg acacgtagat tcgggcaagt ccaccactac tggccatctg
                                                                       120
                                                                       180
atctataaat gcggtggcat cgacaaaaga accattgaaa aatttgagaa ggaggctgct
gagatgggaa agggctcctt caagtatgcc tgggtcttgg ataaactgaa agctgagcgt
                                                                       240
gaacgtggta tcaccattga tatctccttg tggaaatttg agaccagcaa gtactatgtg
                                                                       300
actatcattg atgccccagg acacagagac tttatcaaaa acatgattac agggacatct
                                                                       360
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caggotgact gtgctgtcct gattgttgct gctggtgttg gtgaatttga agctggtatc tccaagaatg ggcaggaccc gagagcatgc ccttctggct tacacactgg gtgtgaaaca actaattgtc ggtgttaaca aaatggatt	420 480 509
<210> 298 <211> 267 <212> DNA <213> Homo sapien	
<220> <221> misc_feature <222> (1)(267) <223> n = A,T,C or G	
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<210> 299 <211> 121 <212> DNA <213> Homo sapien	
<400> 299 ggcacgaggg ccctcggagc tcgtttccag atcgaggtaa gagggacttt cttaaaggcc tagtctatgg gatggggcgg cggagggaat tttttgagaa ataaaatgaa gctgcagtgt a	60 120 121
<210> 300 <211> 533 <212> DNA <213> Homo sapien	
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<210> 301 <211> 560 <212> DNA <213> Homo sapien	
<220> <221> misc_feature	

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<222> (1)...(560)
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cctcggtcaa gatatagtca aataactatg gctgcaggtt ccacagttcc acaataacca
                                                                     120
                                                                     180
tggctgcacg atccacaatt cagacacaga catagagctg gggtgggtgg aaggggcagg
                                                                     240
agggtggcag agtgcggact gtccccagcc ctggcctctc catgcanagt tggcccaggc
                                                                     300
360
gggctgccag gaactgccct tcanaacctt tgggcccagg tcnccctgaa nccccacaac
tttttatctg gaataagtat taaaaaacaa taaattaagc aaacaacntg gnccttgaag
                                                                     420
                                                                     480
gatgttgacc nacatggtcc acagtttttg gcncaaaaaa ataagggctg gtttgctttt
tttggaaggc agggtttgtg gnttggcttt caaatnattt tcaaaccatt ccccagggag
                                                                     540
                                                                     560
gganaacccc cgggggggaa
      <210> 302
      <211> 599
      <212> DNA
      <213> Homo sapien
      <220>
     <221> misc feature
     <222> (1)...(599)
     \langle 223 \rangle n = A, T, C or G
      <400> 302
                                                                      60
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tggaaagact tgtgcacaat agtttcccat ccgtactcag cctctcttgc cccgatcccc
                                                                      180
gacttttcta ctcaaggcca gggaaggcct ccaaggngat gggcggcagg taacgagtca
                                                                     240
ttgcctctca cgccacctgg aaggctggac tacttcctcc tcccaactgc ggggtcccan
aaatcctcgg gtcccagngg ctgacttaca atattcaatt cactctgacc aaacttccta
                                                                      300
tganaaaatc cacggngagc caaaatgaaa agtacaaggc agtagtacag gaacctggca
                                                                      360
                                                                      420
gccgcactgg ccgcccanaa acgtcagtgg ngctgcccca ttcggcgaaa ggttagggag
                                                                      480
caggaaaaga ggaagcagga gagggaagga aagtcccatg gaatatgtat tccanaatcc
                                                                      540
ttacattttc tcagccaccg ctccccacgt gagttcccac ccccaccccg acaagaagca
aagagttctg aggatccaag aacgtgaccg ggtcanacan gttcagctac tgagttcac
                                                                      599
      <210> 303
      <211> 591
      <212> DNA
      <213> Homo sapien
      <400> 303
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cccqcqqqcc gacqccgtac tggaggttgc gcctcggtgg cgccgcgctg ctcctgctgc
                                                                      180
tcatcccqqt qqccqccqcq caggagcctc ccggagctgc ttgttctcag aacacaaaca
                                                                      240
aaacctgtga agagtgcctg aagaacgtct cctgtctttg gtgcaacact aacaaggctt
                                                                      300
gtctggacta cccagttaca agcgtcttgc caccggcttc cctttgtaaa ttgagctctg
cacgctgggg agtttgttgg gtgaactttg aggcgctgat catcaccatg tcggtagtcg
                                                                      360
                                                                      420
ggggaaccct cctcctgggc attgccatct gctgctgctg ctgctgcagg aggaagagga
gccggaagcc ggacaggagt gaggagaagg ccatgcgtga gcgggaggag aggcggatac
                                                                      480
                                                                      540
qqcaqqaqqa acggaqaqca gagatgaaga caagacatga tgaaatcaga aaaaaatatg
                                                                      591
gcctgtttaa agaagaaaac ccgtatgcta gatttgaaaa caactaaagc g
```

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<210> 304
      <211> 441
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
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      <223> n = A, T, C or G
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gtegetgetg etgetgtege egecegegge caeegeetet cagacecage agateeeagg
                                                                       120
cgggtccctg gggtctgtgc tgctgccagc cgccaggttc gatgcccggg aggcggcggc
                                                                       180
                                                                        240
ggcggcgggg gtgctgtacg gaggggacga tgcccagggc atgatggcgg cgatgctgtc
                                                                       300
ccacgcctac ggccccggcg gttgtggggc ggcggcggcc gccctgaacg gggagcaggc
ggccctgctc cggagaaaga gcgtcaacac caccgagtgc gtcccggtgc ccagctccga
                                                                       360
                                                                        420
gcacgtcgcc gagatcgtcg gccgccaggg ttgtaaaatt aaagcactga nagccaagac
                                                                        441
aaacacgtat atcaagactc c
      <210> 305
      <211> 491
      <212> DNA
      <213> Homo sapien
      <400> 305
                                                                         60
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                                                                        120
gggctttgcc tgccacctct gtgggcagag cttccgaggc tgggtggccc tggttctgca
                                                                        180
tetgegggee catteagetg caaageggee categettgt cecaaatgeg agagaegett
                                                                        240
ctggcgacga aagcagcttc gagctcatct gcggcggtgc caccctcccg ccccggaggc
                                                                        300
ccggcccttc atatgcggca actgtggccg gagctttgcc cagtgggacc agctagttgc
ccacaagegg gtgcaegtag etgaggeeet ggaggaggee geageeaagg etetggggee
                                                                        360
                                                                        420
ccggcccagg ggccgccccg cggtgaccgc cccccggccc ggtggagatg ccgtcgaccg
                                                                        480
ccccttccag tgtgcctgtt gtggcaagcg cttccggcac aagcccaact tgatcgctca
                                                                        491
cccgcgcgtg c
      <210> 306
      <211> 547
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(547)
      <223> n = A, T, C or G
      <400> 306
                                                                         60
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                                                                        120
tctacatgta ggaagccaac ctgctccttt ttgatcttct tctttggcac aacctcagtg
gatttctctg attcagaacg agttctaatt gatcttctct gttgcttctt ttctactgag
                                                                        180
cctgtagaac cagatgttgc ttcaggagat gatacactct gcgttggctt ttcatttctc
                                                                        240
                                                                        300
tggtttggtg tagaaattat aagcctgtct tgccccctga cacttatttc tgttttgtta
ccaattccct ttgttgaata aacaaattga tcgataaatt tcccatcccc tgtagcattc
                                                                        360
tgaagagcaa acacttgttc aattttcaca actggagaca tgttacactt ctgcaaatcc
                                                                        420
```

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aggeteeett tgtgeateeg taatggaage tggtaaggat tteettgetg eegeagtttt
                                                                     480
ccaggetatt ttaacaggeg gnggetette etettteege aettgtgtge egeetetgge
                                                                     540
                                                                     547
tatgtct
     <210> 307
     <211> 571
     <212> DNA
     <213> Homo sapien
     <220>
     <221> misc feature
     <222> (1)...(571)
     <223> n = A, T, C or G
      <400> 307
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                                                                      60
gatttcaaat caaccctatt tttaaattac ttttaatagg aanaaatgaa gcaaggacat
                                                                     120
acataatcta ctatatttga aggactcaaa caaatacatg tttggctgtg aattctgtac
                                                                     180
                                                                     240
tctcaccaaa acagagataa aaatccacct aaaatacact ttccttcatt tagtgcttgt
                                                                     300
ggganaaggt caagtattgc actttaaaat tactttcatc taacatttgc cccaactttc
cccctgaatt cactatatgt tttcagcaaa catgatttta taaattttaa gtataaaagc
                                                                     360
                                                                     420
480
aaacggcata tttacttaca aaattganag ataggggcat ccagctgagg tacatttcct
                                                                     540
cccttggcgt tgagtttctg gacttgggtc gggggcacag gcttgtgtga ctgccccgtg
                                                                     571
gcccgataca tggcctggac cccaggatgc g
      <210> 308
      <211> 591
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(591)
      <223> n = A, T, C or G
      <400> 308
                                                                      60
ctccttatgt gtctgcctac ttcattcttc ggcatttcct gcttatccaa gttcaccatt
tcaggtcacc actggatatc agttgcctgt atataattat caggcatttc ctgcttatcc
                                                                     120
                                                                     180
aagttcacca tttcaggtca ccactggata tcagttgcct gtatataatt atcaggcatt
                                                                     240
tcctgcttat ccaagttcac catttcaggt caccactgga tatcagttgc ctgtatataa
ttatcaggca tttcctgctt atccaagttc accatttcag gtcaccactg gatatcagtt
                                                                     300
gcctgtatat aattatcagg catttcctgc ttatccaagt tcaccatttc aggtcaccac
                                                                     360
                                                                     420
tggatatcag ttgcctgtat ataattatca ggcatttcct gcttatccaa gttcaccatt
                                                                     480
tcaggtcacc actggatatc agttgcctgt atataattat caggcatttc ctgcttatcc
                                                                     540
aaattcagca gttcaggtca ccactggata tcagttccat gtatacaatt accagatgcc
                                                                     591
accgcagtgc cctgttgggg gagcaaagga gaaatntgtg gaccgaagca t
      <210> 309
      <211> 591
      <212> DNA
      <213> Homo sapien
      <400> 309
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60
agggggtgca cgtactccca actgtggtcg cgctctcacc ccttctgctg ctctcgtggc
cccctcgcga tggcgggcat cctgtttgag gatattttcg atgtgaagga tattgacccg
                                                                       120
gagggcaaga agtttgaccg aggtaagtaa gtgtctcgac tgcattgtga gagtgaatct
                                                                       180
ttcaagatgg atctaatctt agatgtaaac attcaaattt accetgtaga cttgggtgac
                                                                       240
aagtttcggt tggtcatagc tagtaccttg tatgaagatg gtaccctgga tgatggtgaa
                                                                       300
                                                                       360
tacaacccca ctgatgatag gccttccagg gctgaccagt ttgagtatgt aatgtatgga
                                                                       420
aaagtgtaca ggattgaggg agatgaaact tctactgaag cagcaacacg cctgctgaga
ttgagagctg ctgagtggca gtgctccaga atcacgggat ggggccttct gtttcagctc
                                                                       480
tgcgtacgtg tcctatgggg gcctgctcat gaggctgcag ggggatgcca acaacctgca
                                                                       540
                                                                       591
tggattcgag gtggactcca gagtttatct cctgatgaag aagctagcct t
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      <211> 488
      <212> DNA
      <213> Homo sapien
      <400> 310
tggtctcaag cctgaagagg ctccgcccac aagctggccc atgaagttag caatgcctgt
                                                                        60
                                                                       120
ggcttcagtc aattgtcttg agactgtgaa gaggctgaaa gacaccttcc cgggtggaag
aaggagttca ctgaaaactt atcttaaact gaccetteee tttgagtgag tetteattee
                                                                       180
                                                                       240
tctcccatqt qqqaacccaq cctccqatqc cccggggact aggggaaaca gttggaggtc
                                                                       300
cgtgccqtcc ccaqcctqcc acqqqtqcqa qqacagccaa gtcctgagtg actcaagatg
                                                                       360
cttcacttac atggaagaaa cttctaaaac tctaccgagt ggtttttgta tatactaaag
                                                                       420
ttctatttag agcttttctg ttttgggcaa gttcgctgct ccttctattt gggcactttg
gtttttgtac tgtcttttgt gacggcattg attgaacatt ttttactagt agtcttatga
                                                                       480
                                                                       488
cttttqta
      <210> 311
      <211> 511
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(511)
      <223> n = A, T, C or G
      <400> 311
                                                                        60
cccqtttntg nagcaaaana gggggaagat ttataggtag aggcgacaaa cctaccgagc
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ctggtgatag ctggttgtcc aagatagaat cttagttcaa ctttaaattt gcccacagaa
                                                                       180
ccctctaaat ccccttgtaa atttaactgt tagtccaaag aggaacagct ctttggacac
taggaaaaaa ccttgtagag agagtaaaaa atttaacacc catagtaggc ctaaaagcag
                                                                       240
ccaccaatta agaaagcgtt caagctcaac acccactacc taaaaaaatcc caaacatata
                                                                       300
                                                                       360
actgaactcc tcacacccaa ttggaccaat ctatcaccct atagaagaac taatgttagt
                                                                       420
ataagtaaca tgaaaacatt ctcctccqca taagcctgcg tcagattaaa acactgaact
qacaattaac aqcccaatat ctacaatcaa ccaacaagtc attattaccc tcactgtcaa
                                                                       480
                                                                       511
cccaacacag gcatgctcat aaggaaaggt t
      <210> 312
      <211> 591
      <212> DNA
      <213> Homo sapien
      <400> 312
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<211> 591

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60
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geceageaga aggagaeett gaaatetett ettgaacaag agacagaaaa tttgagaaca
                                                                       120
gaaattagta aactcaacca aaagattcag gataataatg aaaattatca ggtgggctta
                                                                       180
gcagagctaa gaactttaat gacaattgaa aaagatcagt gtatttccga gttaattagt
                                                                       240
agacatgaag aagaatctaa tatacttaaa gctgaattaa acaaagtaac atctttgcat
                                                                       300
                                                                       360
aaccaagcat ttgaaataga aaaaaaccta aaagaacaaa taattgaact gcagagtaaa
                                                                       420
ttggattcag aattgagtgc tcttgaaaga caaaaagatg aaaaaattac ccaacaagaa
gagaaatacg aagctattat ccagaacctt gagaaagaca gacaaaaatt ggtcagcagc
                                                                       480
caggagcaag acagagaaca gttaattcag aagcttaatt gtgaaaaaga tgaagctatt
                                                                       540
                                                                       591
cagactgccc taaaagaatt taaattggag agagaagttg ttgagaaaga g
      <210> 313
      <211> 373
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(373)
      <223> n = A, T, C or G
      <400> 313
                                                                        60
ttgattttta ttctgnattt tattactgaa atangttgtc ctantnatcc caccccacaa
taaaaatntn acccangece ecentteett theetnathe eetntteeae cacaccatee
                                                                       120
cggaacaagt gctccaggat tccctgccca ctggccattt tggagtgtgn ccattgggta
                                                                       180
                                                                       240
gcaatgtgga aaccaccaag gcctttgtgg anaaaatgga gggggttgag ggagncccan
gaggggctna tttgagggcc tttgccactt gctcataggc gagctcnatc tcctcntnat
                                                                       300
                                                                       360
ctgnacangt qqaaqcaaat tcttcccggg cgtnggnant gctnaagnac cgatgcactc
                                                                       373
cccggaaggn ctn
      <210> 314
      <211> 591
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(591)
      <223> n = A, T, C or G
      <400> 314
                                                                         60
cccgtgccgc cgccgcctcc tgggaagaga ggaagcggga gaggagccca cgtcgcctgt
cacccaatat ctccagccgc gcagtcccga agagtgtaag atgttcgcct gcgccaagct
                                                                        120
                                                                        180
cgcctgcacc ccctctctga tccgagctgg atccagagtt gcatacagac caatttctgc
                                                                        240
atcagtgtta tctcgaccag aggctagtag gactggagag ggctctacgg tatttaatgg
                                                                        300
ggcccagaat ggtgtgtctc agctaatcca aagggagttt cagaccagtg caatcagcag
agacattgat actgctgcca aatttattgg tgcaggtgct gcaacagtag gagtggctgg
                                                                        360
                                                                        420
ttctggtgct ggtattggaa cagtctttgg cagccttatc attggttatg ccagaaaccc
ttcgctgaag cagcagctgt tctcatatgc tatcctggga tttgccttgt ctgaagctat
                                                                        480
                                                                        540
gggtctcttt tgtttgatgg ttgctttctt gattttgttt gccatgtaac aaattactgc
ttgacatgtt ggcattcata ttaattacng atgtaattct gtgtatctta c
                                                                        591
      <210> 315
```

```
<212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(591)
      <223> n = A, T, C \text{ or } G
      <400> 315
aagcccttca ccaacaaaga tgcctatact tgtgcaaatt gcagtgcttt tgtccacaaa
                                                                        60
ggctgccgag aaagtctagc ctcctgtgca aaggtcaaaa tgaagcagcc caaagggagc
                                                                       120
cttcaggcac atgacacatc atcactgccc acggtcatta tgagaaacaa gccctcacag
                                                                       180
cccaaggage gtcctcggtc cgcagtcctc ctggtggatg aaaccgctac caccccaata
                                                                       240
tttgccaata gacgatccca gcagagtgtc tcgctctcca aaagtgtctc catacagaac
                                                                       300
attactggag ttggcaatga tgagaacatg tcaaacacct ggaaattcct gtctcattca
                                                                       360
                                                                       420
acagactcac taaataaaat cagcaaggtc aatgagtcaa cagaatcact tactgatgag
                                                                       480
ggtacagaca tgaatgaagg acaactactg ggagactttg agattgagtc caaacagctg
gaagcagagt cttggagtcg gataatagac agcaagtttc taaaacagcc aaaagaaaga
                                                                       540
                                                                        591
tgtgggtcaa acngcgagaa gtaatatatg agttggatgc agacagagtt t
      <210> 316
      <211> 591
      <212> DNA
      <213> Homo sapien
      <400> 316
                                                                        60
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                                                                        120
gtaaatggaa aggagattat gaaaaactgg agcacaacca cacttacatt caatggcttt
tccccctgag agaacaaggc ttgaacttct atgccaaaga actaactaca tatgaaattg
                                                                        180
                                                                        240
aggaattcaa aaaaacaaaa gaagcaatta gaagattcct cctggcttat aaaatgatgc
tagaattttt tggaataaaa ctgactgata aaactggaaa tgttgctcgg gctgttaact
                                                                        300
                                                                        360
ggcaggaaag atttcagcat ctgaatgagt cccagcacaa ctatttaaga atcactcgta
ttcttaaaag ccttggtgag cttggatatg aaagttttaa atctcctctt gtaaaattta
                                                                        420
ttcttcatga agctcttgtg gagaatacta ttcccaatat taagcagagt gctctagagt
                                                                        480
                                                                        540
attttgttta tacaattaga gacagaagag aaaggagaaa gctcctgcgg ttcgcccaga
aacactacac gccttcagag aactttatct ggggacccgc ctcgaaaaga a
                                                                        591
      <210> 317
      <211> 323
      <212> DNA
      <213> Homo sapien
      <400> 317
                                                                         60
ccaagctacg gaagcaagtg gaagagattt ttaatttgaa atttgctcaa gctcttggac
                                                                        120
tcaccgaggc agtaaaagta ccatatcctg tgtttgaatc aaacccggag ttcttctatg
                                                                        180
tggaaggett gccagagggg attecettee gaageeetae etggtttgga attecaegae
ttgaaaggat cgtccacggg agtaataaaa tcaagttcgt tgttaaaaaa cctgaactag
                                                                        240
ttatttccta cttgcctcct gggatggcta gtaaaataaa cactaaagct ttgcagtccc
                                                                        300
                                                                        323
ccaaaagacc acgaagtcct ggg
      <210> 318
      <211> 591
      <212> DNA
      <213> Homo sapien
```

```
<220>
     <221> misc feature
     <222> (1)...(591)
     <223> n = A, T, C or G
     <400> 318
                                                                      60
gatggcgtac ttggcttgga gactggcgcg gcgttcgtgt ccgagttctc tgcaggtcac
tagtttcccg gtagttcagc tgcacatgaa tagaacagca atgagagcca gtcagaagga
                                                                     120
                                                                     180
ctttgaaaat tcaatgaatc aagtgaaact cttgaaaaag gatccaggaa acgaagtgaa
                                                                     240
gctaaaactc tacgcgctat ataagcaggc cactgaagga ccttgtaaca tgcccaaacc
                                                                     300
aggtgtattt gacttgatca acaaggccaa atgggacgca tggaatgccc ttggcagcct
                                                                     360
gcccaaggaa gctgccaggc agaactatgt ggatttggtg tccagtttga gtccttcatt
                                                                     420
ggaatcctct agtcaggtgg agcctggaac agacaggaaa tcaactgggt ttgaaactct
                                                                     480
ggtggtgacc tccgaagatg gcatcacaaa gatcatgttc aaccggccca aaaagaaaaa
tgccataaac actgagatgt atcatgaaat tatgcgtgca cttaaagctg ccagcaanga
                                                                     540
                                                                     591
tgactcaatc atcacttgtt ttaacaggaa atggtgacta ttacagtagn g
      <210> 319
      <211> 591
      <212> DNA
      <213> Homo sapien
      <400> 319
                                                                      60
gaatteggea egaggttget getaagegaa egecetttgg agettaegga ggeettetga
                                                                     120
aagacttcac tgctactgac ttgtctgaat ttgctgccaa ggctgccttg tctgctggca
                                                                     180
aagtctcacc tgaaacagtt gacagtgtga ttatgggcaa tgtcctgcag agttcttcag
                                                                     240
atgctatata tttggcaagg catgttggtt tgcgtgtggg aatcccaaag gagaccccag
                                                                     300
ctctcacgat taataggctc tgtggttctg gttttcagtc cattgtgaat ggatgtcagg
                                                                     360
aaatttgtgt taaagaagct gaagttgttt tatgtggagg aaccgaaagc atgagccaag
                                                                     420
ctccctactg tgtcagaaat gtgcgttttg gaaccaagct tggatcagat atcaagctgg
                                                                     480
aagattettt atgggtatea ttaacagate ageatgteea geteeceatg geaatgaetg
cagagaatct tgctgtaaaa cacaaaataa gcagagaaga atgtgacaaa tatgccctgc
                                                                     540
                                                                     591
agtcacagca gagatggaaa gctgctaatg atgctggcta ctttaatgat g
      <210> 320
      <211> 591
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(591)
      <223> n = A, T, C or G
      <400> 320
                                                                      60
120
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ctcttcaccc tgacctatgg tgccctggtc acccagctat gtaaggacta tgaaaatgat
                                                                     180
                                                                     240
qaaqatgtga ataaacagct ggacaaaatg ggctttaaca ttggagtccg gctgattgaa
                                                                     300
gatttcttgg ctcggtcaaa tgttgggagg tgccatgact ttcgggaaac tgcggatgtc
                                                                     360
attgccaagg tggcgttcaa gatgtacttg ggcatcactc caagcattac taattggagc
                                                                     420
ccagctggtg atgaattctc cctcattttg gaaaataacc ccttggtgga ctttgtggaa
cttcctgata accactcatc ccttatttat tccaatctct tgtgtggggt gttgcgggga
                                                                     480
```

```
gctttggaga tggtccagat ggctngngga ggcccaagtt tgtccaggac accctnaaag
                                                                         540
                                                                         591
gagacgggng tgacagaaat ccggatgaga ttcatcaggc ggattganga c
      <210> 321
      <211> 260
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(260)
      \langle 223 \rangle n = A, T, C or G
      <400> 321
                                                                          60
ctgcttggct ccacacgtgg gccgccgtag gtattccgac cggtaattcc tcctattggt
gtgcagcagc cacattgaag gatagagtgg cagcagaggc caaggatcgt gagttgatgg
                                                                         120
agtttgctgc tgaaaatgaa gggaagtctg ggggaggtct ccacagcgta gctgaggggg
                                                                         180
tgcggctaag tccagagcct ggcagggagg gagtaaggga cttagcaggg gcggaggagt
                                                                         240
                                                                         260
tctgcggngg anaggagggg
      <210> 322
      <211> 559
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(559)
      \langle 223 \rangle n = A, T, C or G
      <400> 322
ttccacatga catggagtgt gaagctggat gagcacatca ttccactggg aagcatggca
                                                                          60
                                                                         120
nttaacagca tctcaaaact gactnanctc acccagtctt ccatgtattc acttcctaat
                                                                         180
gcacccactc tggcanacct gnaggacnat acacatgaag ncantgatga tcagccagan
                                                                         240
aanceteact ttgaeteteg canngtgata tttgagetgg atteatgeaa tggnagtggg
                                                                         300
aaagtttgcc ttgtctacaa aagtgggaaa ccagnattag cagaanacac tgagatctgg
ttcctgnaca nancgttata ctggcatttt ctcacanaca cctttactgc ctattaccgc
                                                                         360
                                                                         420
ctgctcatca cccacctggg cctgccccag tggcaatatg ccttcccagc tatggcatta
                                                                         480
gcccacaggc caagcaatgg ttcagcatgt ataaacctat cacctacaac acaaacctgc
                                                                         540
tcacagaaga naccgactcc tttgtgaata agctagatcc canctnagtg tttaagagca
                                                                         559
agaacaagat cgttatccc
      <210> 323
      <211> 492
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(492)
      <223> n = A, T, C or G
      <400> 323
cctgtctccc agccgtacca gcgagggctc ggccggcagc gccgggctgg ggggcggcgg
                                                                          60
```

```
120
cgccggcgcc ggagccgggg tgggtgcagg cggcggcggg ggcagcggcg cgagcagcgg
cggcggggcc ggggggctgc aacccagcag ccgcgctggc ggcggccggc cctccagccc
                                                                       180
                                                                       240
cagcccgtcg gtggtgagcg agaaggagaa ggaagagttg gagcggctgc agaaagagga
                                                                       300
ggaggagagg aagaagaggc tgcagctgta tgtgttcgtg atgcgctgca tcgcctaccc
ctttaatgcc aagcagccca ccgacatggc tcgccggcag cagaagatca gcaaacagca
                                                                       360
                                                                       420
gctgcagaca gtcaaggacc ggtttcaggc tttcctcaat ggggaaaccc anatcatggc
                                                                       480
tgacgaagcc ttcatgaacc gctgtngcag agttactatg aggtgttcct gaagaccacc
                                                                       492
cgtgtggccg ca
      <210> 324
      <211> 474
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(474)
      <223> n = A, T, C or G
      <400> 324
                                                                        60
aatttcagca acatacttct caatttcttc aggatttaaa atcttgaggg attgatctcg
                                                                       120
cctcatgaca gcaagttcaa tgtttttgcc acctgactga accacttcca ggagtgcctt
                                                                       180
gatcaccage ttaatggtca natcatetgt tteaatgget tegteagtat agttettete
                                                                       240
cagnaactca cgcactgact tggcaccccg gcctatggca ttggccttcc aggcatggta
tgtgcccgag gggtcagtct gatagagcct aggagtgcca tcaaagtcga aacccacgat
                                                                       300
                                                                       360
gagggcagag atgccaaacg gcctgcgccc attgctctgc gtataacgct gcttcanact
ggcgatgtag cgggtgatgt actccacagt gaccgggtcc tccacagtca gccggtggct
                                                                       420
                                                                        474
ctggcactcc acccgggccc tgttgatgac tatccttgca tcggcggtga ggcc
      <210> 325
      <211> 532
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(532)
      <223> n = A, T, C or G
      <400> 325
                                                                         60
gaggagacag gacagagcgt ctggagaggc aggaggacac cgagttcccc gtgttggcct
                                                                        120
ccaggtcctg tgcttgcgga gccgtccggc ggctgggatc gagccccgac aatgggcaac
                                                                        180
gcgcaggagc ggccgtcaga gactatcgac cgcgagcgga aacgcctggt cgagacgctg
                                                                        240
caggeggact egggactget gttggacgeg etgetggege ggggegtget eacegggeea
                                                                        300
gagtacgagg cattggatgc actgcctgat gccgagcgca gggtgcgccg cctactgctg
                                                                        360
ctggtgcagg gcaagggcga ggccgcctgc caggagctgc tacgctgtgc ccagcgtacc
gegggegege eggacecege ttgggaetgg eageaegtgg gteegggeta eegggaeege
                                                                        420
                                                                        480
agctatgace etceatgece aggeeactgg aegeeggagg caeeeggete ggggaecaca
                                                                        532
tgccccgggt tgcccagact tcagaccctg acgaggncgg gggccctgag gg
      <210> 326
      <211> 322
      <212> DNA
      <213> Homo sapien
```

```
<220>
      <221> misc feature
      <222> (1)...(322)
      \langle 223 \rangle n = A,T,C or G
      <400> 326
                                                                         60
caaaattaac atttttatta aatcaagtta aaaaaaatgt tcagtgtana aaagtcaaca
agggttttaa caaaaccaaa atataccttt ttatacaata tatgtatata ttagcagcaa
                                                                        120
                                                                        180
actacttctg anattctctt tcttttatgt tcttctagtt attttaaaga aagcataaac
aatgtatatt agtatggaat gtcagcaaat ccactcttag tcctttattc tgtgatttgg
                                                                        240
gccttctaca aaatactttg tgattctcac taatgaatat taagaacata cccaatttta
                                                                        300
                                                                        322
actaaaaaqt agtgaaacag tg
      <210> 327
      <211> 387
      <212> DNA
      <213> Homo sapien
      <400> 327
                                                                         60
aaaaccgtgt actattagcc atggtcaacc ccaccgtgtt cttcgacatt gccgtcgacg
                                                                        120
qcqaqccctt gggccgcgtc tcctttgagc tgtttgcaga caaggtccca aagacagcag
aaaattttcg tgctctgagc actggagaga aaggatttgg ttataagggt tcctgctttc
                                                                        180
                                                                        240
acagaattat tccagggttt atgtgtcagg gtggtgactt cacacgccat aatggcactg
gtggcaagtc catctatggg gagaaatttg aagatgagaa cttcatccta aagcatacgg
                                                                        300
                                                                        360
qtcctggcat cttgtccatg gcaaatgctg gacccaacac aaatggttcc cagtttttca
                                                                        387
tctgcactgc caagactgag tggttgg
      <210> 328
      <211> 502
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(502)
      <223> n = A, T, C or G
      <400> 328
                                                                         60
agcagcccgg cgcggccgcc gcgccggcgg gcggcaaggc tccgggccag catgggggct
                                                                        120
tcgtggtgac tgtcaagcaa gagcgcggcg agggtccacg cgcgggcgag aaggggtccc
                                                                        180
acgaggagga gccggtgaag aaacgcggct ggcccaaggg caagaagcgg aagaagattc
tgccgaatgg gcccaaggca ccggtcacgg gctacgtgcg cttcctgaac gagcggcgcg
                                                                        240
agcagatccg cacgegecac ceggatctge cettteeega gateaccaag atgetgggeg
                                                                        300
                                                                        360
ccgagtggag caagctgcag ccaacggaaa agcagcggta cctggatgag gccnagagag
agaagcagca gtacatgaag gagctgcggg cgtaccagca gtctgaagcc tataagatgt
                                                                        420
                                                                        480
gcacggagaa gatccaggag aagaagatca agaaagaaga ctcgagctct gggctcatga
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acactettet gaatggacae aa
      <210> 329
      <211> 463
      <212> DNA
      <213> Homo sapien
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<220>
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      <223> n = A, T, C or G
      <400> 329
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aagtoottta tacaaaataa ggacaatttg taaaganaat ccactgtcat gttttgoott
                                                                        120
gtcaagtcaa aactcaaata gcttgttttg gtaaaattat tccagaaaca taatccagac
                                                                       180
                                                                       240
aaaatcaata acgtcatcag cttcctaacc atgtttaana ggaataactt catgaacatt
                                                                        300
ttgccctgaa ctgaanagtt ctaaatactt gtaaaccttt aggaaaaaat gactgctcgc
aggcagcttg actggtaaga gggtacacca nagactccgg gtcactcact gtcagaatat
                                                                        360
                                                                        420
tottatacat acaatgagto tocacgootg tacaatgagt gtogtgcaac ataattggag
                                                                        463
taatggcctc taaaatttta caagtaaact ttattgnggc ccc
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      <211> 500
      <212> DNA
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      <220>
      <221> misc feature
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      <223> n = A, T, C \text{ or } G
      <400> 330
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caaaaggact ataaaacaaa aacagagaag aaaattcatg gctaaaccag ctgaagaaca
                                                                        120
gcttgatgtg ggacagtcta aagatgaaaa catacataca tcacatatta cccaagacga
                                                                        180
                                                                        240
atttcaaaga aattcagaca gaaatatgga agagcatgaa gagatgggaa atgattgtgt
ttccaaaaaa acagatgcca cctgtgggaa gcaagaaaag tagcactaga aaagataagg
                                                                        300
aagaatctaa aaagaagcgc ttttccagtg agtccaagaa caaacttgtn cctgaagaag
                                                                        360
                                                                        420
tgacttcaac tgtcacgaaa agtcgaanaa tttccangcg tccatctgat tggtgggtgg
                                                                        480
taaaancaga ggagagteet gtttatagea attetteagt aagaaatgaa ttaecaantg
                                                                        500
catcacaatn ntgcccggaa
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      <211> 494
      <212> DNA
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      <221> misc feature
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      <400> 331
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tgaattcact taggatcgca ggaatcaggg gaaagtgatt ttaaaggtgg tttctccagc
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acattttaag aaaagggacc aaaagttatt ttagcttcct caatagattg catgttgctt
                                                                        180
attaggataa taaattaata ttaaatgcaa tatatgtctt gnctttatta tggcatctat
                                                                        240
                                                                        300
ttaggagttg ttcaaatcac tgcagtaggg ctctgcaaat aaaataatgn aacctattat
                                                                        360
catggatcta atgnactgna actttatcag tgaaaggnaa aatctcaaat aacaagtaca
aacattggac aattacctat aaagatttgt aaaaggaaaa tttttccata gatttcattc
                                                                        420
```

ttggcatttt gtaaagacga ccctgcagnc ccctgtttgn aactttttta ataaaataga catctgttta cttg	480 494					
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<pre>&lt;400&gt; 332 aaagaacaaa tggaacgcga tggttgttct gaacaagagt ctcaaccgtg tgcatttatt gggataggaa atagtgacca agaaatgcag cagctaaact tggaaggaaa gaactattgc acagccaaaa cattgtatat atctgactca gacaagcgaa agcacttcat gttgtctgta aagatgttct atggcaacag tgatgacatt ggtgtgttcc tcagcaagcg gataaaaagtc atctccaaac cttccaaaaa gaagcagtca ttgaaaaatg ctgacttatg cattgcctca ggaacaaagg tggctctgtt taatcgacta cgatcccaga cagttagtac cagatacttg catgtagaag gaggtaattt tcatgccagt tcacagcagt ggggagcctt ttttattcat ctcttggatg atgatgaatc agaaggagaa gaattcacag tccgagatgg ctacatccat tatggacaaa cagtcaaact tgtgtgctca gttactggca tggcactcc aagattga</pre>	60 120 180 240 300 360 420 480 538					
<210> 333 <211> 499 <212> DNA <213> Homo sapien						
<pre>&lt;400&gt; 333 ctcagcctgc gggactgctc ggctcggctt ctaggcggtt ttgatgaaca cctggcttta ttcttgcaat gaagaaaggt tctcaacaaa aaatattctc caaagcaaag</pre>	60 120 180 240 300 360 420 480 499					
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ctcaatcatc actgttttaa cangaaatgg tgactattac agtagtggga atgatctgac taacttcnct gatattcccc c	540 561
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<210> 336 <211> 540 <212> DNA <213> Homo sapien <220> <221> misc_feature	
<222> (1)(540) <223> n = A,T,C or G	
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<210> 337 <211> 422 <212> DNA <213> Homo sapien	
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180
gctggagctc atgccggtgg acctggggtc agagcaggag ctggagcagc agcggcagga
gttggagcgg cagcaggagc tggaacggca gcaggagcag cggcagctgc agctcaaact
                                                                       240
                                                                       300
gcaggaggag ctgcagcagc tggagcaaca gctggagcag cagcagcagc agctggagca
gcaggaggtg cagctggagc tgaccccggt ggagctaggc gcccagcagc aggaggtgca
                                                                       360
                                                                       420
gctggagctg acccccgtgc agccggagct gcagctggaa ctggtgccan cccagggggc
                                                                       422
gg
      <210> 338
      <211> 601
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(601)
      <223> n = A, T, C or G
      <400> 338
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gctctatgat gtcagcctac gagcgctcta tgatgtcagc ctacgagcgc tctatgatgt
                                                                        180
cccctatggc tgagcgctct atgatgtcag cttatgaacg ctccatgatg tcagcttatg
                                                                        240
aacgctccat gatgtcccca atggctgatc gatctatgat gtccatgggt gctgaccggt
ctatgatgtc gtcatactct gctgctgacc ggtctatgat gtcatcgtac tctgcagctg
                                                                        300
accgatctat gatgtcatct tatactgctg atcgttcaat gatgtctatg gctgctgatt
                                                                        360
cttacaccga ttcttacact gacacatata cagaggcata tatggtgcca cctttgcctc
                                                                        420
                                                                        480
ctgaagagcc cccaacaatg ccaccgttgc cacctgagga gccaccaatg acaccaccat
                                                                        540
tgcctnctga ggaaccaccc agagggtcca gcattgccca cttgagcagt cagcattaac
cagcttgaaa atacttggcc ctacanangg tgccatcatt accatctgaa gagctgtatc
                                                                        600
                                                                        601
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      <211> 440
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(440)
      <223> n = A, T, C or G
      <400> 339
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tattgctgat actctagtgg ggctggaagg gtggttccta ttcgcaccat cgccaaccag
                                                                        120
agacagaggg aaaaaaaaa ccggcagcca ctgctgatgt tgggttcgga ggctgcatcc
                                                                        180
gacteggtea caaggaaaat ggatteagtt tgeatetete eeteetttaa acagettete
                                                                        240
                                                                        300
cgggtctcag catggtatca aagcttgaaa gagagaagac tcaagaagcg aagaggattc
gtgagctgga gcagcgcaag cacacggtgc tggtgacaga actcaaagcc aagctccatg
                                                                        360
                                                                        420
aggagaagat gaaggagctg caggctgtga gggagaacct tatcaagcag cacgacagga
                                                                        440
aatgtcaang acggtgaagg
      <210> 340
      <211> 450
      <212> DNA
      <213> Homo sapien
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<211> 491

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      <222> (1)...(450)
      <223> n = A, T, C or G
      <400> 340
                                                                         60
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aggatteete aggeegaeea gtggaagtet teaaaeaaga geetggtgga ggetetgggg
                                                                        120
ctggaagccg agggtgcagt tcctgagaca cagactttga ccggatggag taaggggttc
                                                                        180
attggcatgc acagggaaat gcaagtcaac cccatttcaa agcggatggg gcccatgact
                                                                        240
                                                                        300
gtggtcagga tggacgcttc agtccagcca ggcccttttc ggaccctgct ccagtttctt
tatacgggac aactggatga aaaggaaaag gatttggtgg gcctggctca gatcgcagag
                                                                        360
                                                                        420
gtcctcgaga tgttcgattt gaggatgatg gtggaaaaca tcatgaacaa ggaagccttc
                                                                        450
atgaaccagg agattacgaa nncctttcac
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      <211> 451
      <212> DNA
      <213> Homo sapien
      <400> 341
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cateceatga ggatetgeec getteecagg aaaggteega ggttaateea geaegtatgg
                                                                        120
ggccaagtgt aggctcccag caggaactga gagcgccatg tettccagta acctatcagc
                                                                        180
                                                                        240
agacaccagt gaacatggaa aagaacccaa gagaggcacc teetgttgtt eeteetttgg
caaatgctat ttctgcagct ttggtgtccc cagccaccag ccagagcatt gctcctcctg
                                                                        300
                                                                        360
ttcctttgaa agcccagaca gtaacagact ccatgtttgc agtggccagc aaagatgctg
gatgtgtgaa taagagtact catgaattca agccacagag tggagcagag atcaaagaag
                                                                        420
                                                                        451
ggtgtgaaac acataaggtt gccaacacaa g
      <210> 342
      <211> 498
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(498)
      \langle 223 \rangle n = A, T, C or G
      <400> 342
                                                                         60
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                                                                        120
actgatactc caaacaagaa accaactaaa ggcaaaggta aaaaacatga agcagatgag
                                                                        180
ttgagtggag atgcttctgt gggaagatga tgcttttatc aaggactgtg aattggagaa
                                                                        240
tcaaqaqqca catqaqcaaq atggaaatga tgaactaaaq gactctgaag aatttggtga
aaatgaagaa gaaaatgtgc attccaagga gttactctct gcagaagaaa acaagagagc
                                                                        300
                                                                        360
tcatgaatta atagaggcag aaggaataga agatatagaa aaagaggaca tcgaaagtca
                                                                        420
ggaaattgaa gctcaagaag gtgaagatga tacctttcta acagcccaag atggtgagga
                                                                        480
aqaaqaaaat gagaaagata tagcagggtt ctggtgatgg cncacaagaa gtatntaaac
                                                                        498
ctcttccttc aaaaaggg
      <210> 343
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<212> DNA
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gtatgaacat ggcagcagcc gcggcccacc accaccacca ccaccaccac caccccggtg
                                                                       120
                                                                       180
cctttttccg ctatatgcgg cagcagtgca tcaagcagga gctaatctgc aagtggatcg
                                                                       240
accccgagca actgagcaat cccaagaaga gctgcaacaa aactttcagc accatgcacg
agctggtgac acacgtctcg gtggagcacg tcggcggccc ggagcagagc aaccacgtct
                                                                       300
gcttctggga ggagtgtccg cgcgagggca agcccttcaa ggccaaatac aaactggtca
                                                                       360
accacatecg egtgeacaea ggegagaaae cetteeetge eetteegggt gtggeaaagt
                                                                       420
                                                                       480
cttcgcgcgc tccgagaacc tcaagatcca caaaaggacc acacagggga gaagccgtcc
                                                                       491
agtggagttg a
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      <211> 412
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
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      <400> 344
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gatgaaggca aactttttgt tggagggctg agttttgaca ccaatgagca gtcgctggag
caggtcttct caaagtacgg acagatctct gaagtggtgg ttgtgaaaga cagggagacc
                                                                       180
cagagatete ggggatttgg gtttgtcace tttgagaaca ttgacgaege taaggatgee
                                                                        240
atgatggcca tgaatgggaa gtctgtagat ggacggcaga tccgagtaga ccaggcaggc
                                                                        300
                                                                       360
aagtcgtcan acaaccgatc ccgtgggtac cgtggtggct ctgccggggg ccggggcttc
ttccgtgggg gcccgangac ggggcccgtg ggttctctaa aagaagaggg ga
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                                                                        120
                                                                        180
agctgcgata atgtgaaggt tgttgttagg tgccggcccc tcaatgagag agagaaatca
atgtgctaca aacaggctgt cagtgtggat gagatgaggg gaactatcac tgtacataag
                                                                        240
actgattctt ccaatgaacc tccaaagaca tttacttttg atactgtttt tggaccagag
                                                                        300
                                                                        360
aqtaaacaac ttqatqttta taacttaact gcaagaccta ttattgattc tgtacttgaa
                                                                        420
ggctacaatg ggactatttt tgcatatgga caaaccggaa caggcaaaac ttttaccatg
gaaaggtgtc gagctattcc tgaacttaga ggaataattc cccaatttct ttgctcacaa
                                                                        480
                                                                        498
tatttgggcc atatttgc
      <210> 346
      <211> 427
      <212> DNA
      <213> Homo sapien
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      <222> (1)...(427)
      \langle 223 \rangle n = A, T, C or G
      <400> 346
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                                                                        180
tccaagccag attgctggcc ctttctggtc ctggtggagg tagaggacgt ggtagtttat
                                                                        240
tactgaggcg tggattctca gatagtggag gaggaccccc agccaaacag agagaccttg
                                                                        300
aaggggcagt cagtaggctg ggcggggagc gtcggaccag aagagaatca cgccaggaaa
                                                                        360
gcgacccgga ggatgatgat gttaaaaagc cagcattgca gtcttcannt gtagctacct
                                                                        420
cccaaagagc gccccacgta gagaccttat ccagggatca aaattttgga tgaaaaaggg
                                                                        427
gaaagcc
      <210> 347
      <211> 280
      <212> DNA
      <213> Homo sapien
      <400> 347
                                                                         60
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agcaggcatc gtgggaaggt gaagagcttc cctaaggatg acccgtccaa gccggtccac
                                                                        180
ctcacagect teetgggata caaggetgge atgaeteaca tegtgeggga agtegaeagg
                                                                        240
ccgggatcca aggtgaacaa gaaggaggtg gtggaggctg tgaccattgt agagacacca
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cccatggtgg ttgtgggcat tgtggggctac gtggaaaccc
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      <211> 411
      <212> DNA
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ggatgcaatc cattccatgg gttttattca cagagatgtg aagcctgata acatgctgct
                                                                        120
ggataaatct ggacatttga agttagcaga ttttggtact tgtatgaaga tgaataagga
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                                                                        240
aggcatggta cgatgtgata cagcggttgg aacacctgat tatatttccc ctgaagtatt
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aaaatcccaa ggtggtgatg gttattatgg aagagaatgt gactggtggt cggttggggt
                                                                        360
atttttatac gaaatgcttg taggtgatac acctttttat gcagattctt tggttggaac
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      <210> 349
      <211> 408
      <212> DNA
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ctaccacaag aagcggaagt atgagttggg gcgcccagct gccaacacca agattggccc
ccgccgcatc cacacagtcc gtgtgcgggg aggtaacaag aaataccgtg ccctgaggtt
                                                                        180
                                                                        240
ggacgtgggg aatttctcct ggggctcaga gtgttgtact cgtaaaacaa ggatcatcga
                                                                        300
tgttgtctac aatgcatcta ataacgagct ggttcgtacc aagaccctgg tgaagaattg
                                                                        360
categigete ategacagea cacegiaceg acagiggiae gagicecaet atgegetgee
                                                                        408
cctgggccgc aagaagggag ccaaactgac ttctgaggaa gaagaaaa
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      <212> DNA
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gtgctcgtgc tcagccagaa cacaaagcgt gaatccggaa gaaaagttca atctggaaac
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atcaatgctg ccaagactat tgcagatatc atccgaacat gtttgggacc caagtccatg
                                                                       180
atgaagatgc ttttggaccc aatgggaggc attgtgatga ccaatgatgg caatgccatt
                                                                       240
                                                                       300
cttcgagaga ttcaagtcca gcatccagcg gccaagtcca tgatcgaaat tagccggacc
caggatgaag aggttggaga tgggaccaca tcagtaatta ttcttgcagg ggaaatgctg
                                                                       360
                                                                       409
tetgtagetg agcaetteet ggageageag atgeaceeaa eaggtgggg
      <210> 351
      <211> 226
      <212> DNA
      <213> Homo sapien
      <400> 351
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agaactaatg ttagtataag taacatgaaa acatteteet eegeataage etgegteaga
                                                                       180
ttaaaacact gaactgacaa ttaacagccc aatatctaca atcaaccaac aagtcattat
                                                                        226
taccctcact gtcaacccaa cacaggcatg ctcataagga aaggtt
      <210> 352
      <211> 410
      <212> DNA
      <213> Homo sapien
      <400> 352
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                                                                         60
                                                                        120
cttgaaggag gagctgctca aagccatctg gcacgccttc accgcactcg accaggacca
                                                                        180
cagcggcaag gtctccaagt cccagctcaa ggtcctttcc cataacctgt gcacggtgct
                                                                        240
gaaggtteet catgacccag ttgcccttga agagcactte agggatgatg atgagggtee
agtgtccaac cagggctaca tgccttattt aaacaggttc attttggaaa aggtccaaga
                                                                        300
                                                                        360
caactttgac aagattgaat tcaataggat gtgttggacc ctctgtgtca aaaaaaacct
cacaaagaat cccctgctca ttacagaaga agatgcattt aaaatatggg
                                                                        410
      <210> 353
      <211> 380
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(380)
      <223> n = A, T, C or G
      <400> 353
                                                                         60
gagtttattt agaaagtatc atagtgtaaa caaacaaatt gtaccacttt gattttcttg
gaatacaaga ctcgtgatgc aaagctgaag ttgtgtgtac aagactcttg acagttgtgc
                                                                        120
ttctctagga ggntgggttt ttttaaaaaa agaattatct gngaaccata cgtgattaat
                                                                        180
```

```
240
aaagatttcc tttaaggcan aggctggtcn agatgctgct gttatcttct gcctcagaca
gacagtataa gnggtcttgt ttctaagatt cctaccacca gttactttgg gccaagtatc
                                                                       300
cacatcccct tgcgtatggg aggngggtga anagtgttgg atgcaaagng gttattatgg
                                                                       360
                                                                       380
qaaqnaqctc natqqtaaaa
      <210> 354
      <211> 379
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(379)
      <223> n = A, T, C or G
      <400> 354
                                                                         60
caacacatct ttattaaaca cctgaagtta ctgggaggag gccatgatgc tggacacact
gtcaaagtca atcttctcca caatgttctt gggtttaatg ctctcttctt ggctacagan
                                                                        120
gaanatotgo cocgactngt oggoactoca googtatttg otoatocaca cotttagotg
                                                                        180
                                                                        240
gctgtccgac aganccccga gcatntcggc cagcagccan cggncaatgt gctggtaagt
gatacccaca acatggcaga taaactttcg gacanagtct tcaaagccag ttataccttc
                                                                        300
                                                                        360
caagaggtcc atgttttcat ccagggcttg ccanaagcct ggaaatggca ggtctccaac
                                                                        379
aggtccccca ggtacaaaa
      <210> 355
      <211> 499
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(499)
      <223> n = A, T, C or G
      <400> 355
                                                                         60
gtccagagct gctggtgctc ccgttcccca gaccctaccc ctatccccag tggagccgga
gtgcgggcgc gccccaccac cgccctcacc atggtgctgt tggcagcagc ggtctgcaca
                                                                        120
                                                                        180
aaagcaggaa aggctattgt ttctcgacag tttgtggaaa tgacccgaac tcggattgag
                                                                        240
ggcttattag cagcttttcc aaagctcatg aacactggaa aacaacatac gtttgttgaa
                                                                        300
acagagagtg taagatatgt ctaccagcct atggagaaac tgtatatggt actgatcact
                                                                        360
accaaaaaca gcaacatttt agaagatttg gagaccctaa ggctcttctc aagagtgatc
                                                                        420
cctqaatatt gcgagcctta gaagagaatg aaatatctga gcactgnttt gatttgattt
                                                                        480
ttgcttttga tgaaaatgtc gcactgggat acccgggang aatgttaact tggcacagat
                                                                        499
canaaccttt cacagaaaa
      <210> 356
      <211> 511
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(511)
      <223> n = A, T, C or G
```

<210> 359 <211> 511

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<400> 356
gggcttctgc tgagggggca ggcggagctt gaggaaaccg cagataagtt tttttctctt
                                                                        60
tgaaagatag agattaatac aactacttaa aaaatatagt caataggtta ctaagatatt
                                                                       120
gcttagcgtt aagtttttaa cgtaatttta atagcttaag attttaagag aaaatatgaa
                                                                       180
                                                                       240
gacttagaag agtagcatga ggaaggaaaa gataaaaggt ttctaaaaca tgacggaggt
                                                                       300
tgagatgaag cttcttcatg gagtaaaaaa tgtatttaaa agaaaattga gagaaaggac
                                                                       360
tacagagece egaattaata eeaatagaag ggeaatgett ttagattaaa atgaaggtga
cttaaacagc ttaaagttta ntttaaaagt tgtaggtgat taaaataatt tgaaggcgat
                                                                       420
                                                                       480
cttttaaaaa gagattaaac ccgaaggtga ttaaaagacc ttgaaatcca tgacgccagg
                                                                       511
gagaattgcc gtcatttaaa gcctagttaa c
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      <211> 511
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(511)
      <223> n = A, T, C or G
      <400> 357
gatacttcac atttccctag ggacgggagc ccgaggggtc cgttcggccc tcttcctctc
                                                                         60
getgggeega cacceegetg taggacegta accettagte ceaatgeete egtaagegga
                                                                        120
gttgagtggg tgcctgtggt tggagctgtg gaggtgtccc cggtggcgag cgcggccaga
                                                                        180
                                                                        240
actgcggtca cttaagtttt ccgtgtgcgg gttgcaagga gcgtgcgtgc gtctggtata
                                                                        300
atttggcttc ctgagattct gcttacaaga aaggagtggg aaataccctt ggaaagaaaa
ctaaaacagt aagaaaacca aaacttattt ttacatggnt gtcagcacat ttaccgatat
                                                                        360
                                                                        420
ggacactttt cccaataatt tcctcctggt ggagacagtg gattgacagg ttctcagtcg
                                                                        480
gaattccaga aaaatgttaa ttgatgaaaa gggtacnatg tgagcatcat aaagntaatt
                                                                        511
attaanacac tgaaggctga acacacaagg g
      <210> 358
      <211> 401
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(401)
      <223> n = A, T, C or G
      <400> 358
                                                                         60
acggatgaag atgatgacct tcaagaaaat gaagacaata aacaacataa agaaagcttg
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aaaagagtga cctttgcttt accagatgat gcggaaactg aagatacagg tgttttaaat
gtaaagaaaa attctgatga agttaaatcc tcctttgaaa aaagacagga aaagatgaat
                                                                        180
                                                                        240
gaaaaaattg catctttaga aaaagagttg ttagaaaaaa agcccgtggc agcttcaggg
                                                                        300
ggaagtgaca gcacagaaga ggccagagaa cacctectgg aggagaceet acetttgeca
tctgcccgat ggccctgtga ttacagagga acccccttca ctggagattt ctttaacnga
                                                                        360
                                                                        401
ngatagagat engnttggga tatgtnteet taagaaaace t
```

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<212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(511)
      <223> n = A, T, C \text{ or } G
      <400> 359
                                                                         60
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                                                                        120
gcgctgctgc tgctgctgct gggccatggc ggcggcgggc gctggggcgc ccgggcccag
                                                                        180
gaggeggegg eggeggege ggaegggeee eeegeggeag aeggegagga eggaeaggae
                                                                        240
ccgcacagca agcacctgta cacggccgac atgttcacgc acgggatcca gagcgcccgc
                                                                        300
geacttegte atgttetteg egecetggtg tggacaettg ceageggett geageegant
                                                                        360
ttggaatgac cttggganga acaaatacaa cagcatggaa agaatgccaa aagtctatgt
                                                                        420
ggnttaaagt ggacttgcac nggccacttc gactngtgct cccccaaggg gngggaagat
                                                                        480
acccacctta aaacttttca accaagccaa aaactttgaa aaccaggtct cggattcaaa
                                                                        511
atggaaaact gatgttcaac ctgaacaaga a
      <210> 360
      <211> 511
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(511)
      <223> n = A, T, C or G
      <400> 360
                                                                         60
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tagacagcaa gtttctaaaa cagcaaaaga aagatgtggt caaacggcaa gaagtaatat
                                                                        120
atgagttgat gcagacagag tttcatcatg tcccgactct caagatcatg agtggtgtgt
                                                                        180
                                                                        240
cnagccnggg gatgatggcg gatctgnttt ttgagcanca gatggtagaa aaagctggtt
                                                                        300
ccctgtttgg atgagettga teagtateee atacceatte ttteeagagg attettggag
                                                                        360
ccggaaagaa nggagtcttc ttggtgggat aaaaagtgaa aaagaacttt ctcttcaana
                                                                        420
aggatagggg gatgtgcttt gtaaaatcan tttttcaggg ngganaatgc cnnaaccgtt
                                                                        480
ttaaagaaaa acatnttggg naagtttttg tgggccaaca ttacccggtc ttgtaaacct
                                                                        511
accttcaaag aacctttttg cccagggtta a
      <210> 361
      <211> 411
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(411)
      <223> n = A, T, C or G
      <400> 361
                                                                         60
gctcagcggc ccgatcccac ggaagcgcgc tcggaggggt gggacccggc cggaccggag
                                                                        120
atggcgccgc cagcgggcgg ggcggcggcg gcggcctcgg acttgggctc cgccgcagtg
ctcttggctg tgcacgccgc ggtgaggccg ctgggcgccg ggccagacgc cgaagcacaa
                                                                        180
```

```
240
cttgcggagg ctgcagctta acgcggaccc tgagaagcct ggcgcttncn gctggaactt
cttggcgcgg gacctggggc ggtaatttga gtggccctga gtcatttcta caccatccag
                                                                       300
gcccaccaca cgactaagct cacaagaagg ctgaactnne tgattetnaa ectagaanta
                                                                       360
                                                                       411
cgtgcatcta tcagtgccng aagaaatgac aacataccac tggcaactct g
      <210> 362
      <211> 511
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(511)
      <223> n = A, T, C or G
      <400> 362
                                                                        60
egggggaceg ggetgeettg geceeteage getegegtet ttteeggeag ttggaacget
                                                                       120
tectgttgte etcaceegta acceetgtt geceetgte teagagteee teaegegtee
cetecegtet ttggetegtt ggetgeegee geeggggett egeeageett caagtegaga
                                                                       180
ctactggccg aaggggcgtc tgcggctctc cgccgtcccc agccctgcct ctccctgggc
                                                                       240
                                                                       300
tctgccatgg caatgacagg ctcaacacct tgctcatcca tgagtaacca cacaaaggaa
                                                                       360
agggtgacaa tgaccaaaag tgacactgga gaatttttat agcaacctta tcgctcacat
                                                                        420
gaagaacgag aaatgagaca aaagaagtta gaaaaagggg atggaagaag aaggcctaaa
aaaatgaagg agaaaaccaa cttccgaaga tcaaccacat tgcttcggaa anggaaacaa
                                                                        480
                                                                        511
aantttcttt cgtttgaaan aaaaacaaan a
      <210> 363
      <211> 401
      <212> DNA
      <213> Homo sapien
      <400> 363
caggatetgg ggagaaagag ceceateeet tetetetetg ceaceattte ggacaeeeeg
                                                                         60
                                                                        120
cagggactcg ttttgggatt cgcactgact tcaaggaagg acgcgaaccc ttctctgacc
                                                                        180
ccagctcggg cggccacctg tctttgccgc ggtgaccctt ctctcatgac cctgcggtgc
cttgagccct ccgggaatgg cggggaaggg acgcggagcc agtgggggac cgcggggtcg
                                                                        240
geggaggage cateceegea ggeggegegt etggegaagg eeetgeggga geteggteag
                                                                        300
                                                                        360
acaggatggt actggggaag tatgactgtt aatgaagcca aagagaaatt aaaagaggca
                                                                        401
ccagaaggaa ctttcttgat tagagatagc tcgcattcag a
      <210> 364
      <211> 401
      <212> DNA
      <213> Homo sapien
      <400> 364
                                                                         60
agtcaaaggt ttcttttccc tttttaccat ggtttctaca aaaataacct tcaggaaaaa
                                                                        120
gaaaatcagg aaaaaaattt tttttcaata atcttattcc ctatattaaa ttagatttga
                                                                        180
agaggattaa cgttgtttta gtttgggtcc agatcagcct tatacaacat ttctaaactc
                                                                        240
atttgtactt ttaaaaaatt taaacacaga cttctaaaat tacttgatgt aagtaattta
                                                                        300
aatcacttat gaccaagtta ttaaccttat gaatcagaag tctgaccctt gtaggaaatt
                                                                        360
atattcacat ataaagtaca tcagatcttt gccatatatt gatggttatt atgcataaac
                                                                        401
acattgagtt gtgttggaag cagatttata aacctgcatg t
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<210> 365
      <211> 361
      <212> DNA
      <213> Homo sapien
      <400> 365
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ttacattcag catttaagag aggcagtaca aaaatgtgtt ctgcttttat ctgatataaa
                                                                       120
ttgcatgtaa taccatgatt taaacaatat cagttatatt aactaatgcc atgagatata
                                                                       180
                                                                       240
tottactcag aacgtotgat gtttcccata atagacagaa aaaatgcagt tgtatgagca
                                                                       300
actgagtttc ttttcatctt caaattcatt tgtgatggtg ggaagatcta aggacaatcc
                                                                       360
ttccattgaa gaagtaggaa aaacagttca gcactgttct gaactcatca aaaatgaaat
                                                                       361
      <210> 366
      <211> 401
      <212> DNA
      <213> Homo sapien
      <400> 366
                                                                        60
cgggagcagc agaggtctag cagccgggcg ccgcgggccg ggggcctgag gaggccacag
                                                                       120
gacgggcgtc ttcccggcta gtggagcccg gcgcggggcc cgctgcggcc gcaccgtgag
                                                                       180
gggaggaggc cgaggaggac gcagcgccgg ctgccggcgg gaggaagcgc tccaccaggg
                                                                       240
cccccgacgg cactcgttta accacatccg cgcctctgct ggaaacgctt gctggcgcct
                                                                        300
gtcaccggtt ccctccattt tgaaagggaa aaaggctctc cccacccatt cccctgcccc
                                                                        360
taggagetgg ageeggagga geegegetea tggegtteag eeegtggeag ateetgteee
                                                                        401
ccgtgcagtg ggcgaaatgg acgtggtctg cggtacgcgg c
      <210> 367
      <211> 401
      <212> DNA
      <213> Homo sapien
      <400> 367
                                                                         60
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acagatectg aaggatatgg gaateacaga gtatgaacca agggttataa ateaaatgtt
                                                                        120
                                                                        180
ggaatttgct ttccgttatg tgactacaat tctggatgat gcaaaaattt attcgagcca
                                                                        240
tgctaagaaa cctaatgttg atgcagatga tgtgagactg gcaatccagt gtcgtgctga
                                                                        300
ccaatctttt acctctcctc ccccaagaga ttttttactg gatatcgcaa ggcagaaaaa
                                                                        360
tcaaacccct ttgccactga ttaagccata tgcaggacct agactgccac ctgatagata
                                                                        401
ctgcttaaca gctccaaact ataggctgaa gtccttaatt a
      <210> 368
      <211> 401
      <212> DNA
      <213> Homo sapien
      <400> 368
                                                                         60
cggagcggta ggagcagcaa tttatccgtg tgcagcccca aactggaaag aagatgctaa
                                                                        120
ttaaagtgaa gacgctgacc ggaaaggaga ttgagattga cattgaacct acagacaagg
                                                                        180
tggagcgaat caaggagcgt gtggaggaga aagagggaat ccccccacaa cagcagaggc
                                                                        240
tcatctacag tggcaagcag atgaatgatg agaagacagc agctgattac aagattttag
gtggttcagt ccttcacctg gtgttggctc tgagaggagg aggtggtctt aggcagtgat
                                                                        300
```

```
ggacceteca ttttacetet ttaccetgte geteataatg aggeateata tateetetea
                                                                        360
                                                                        401
ctctctggga caccatagcc ctgcccctc ccctggatgc c
      <210> 369
      <211> 174
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(174)
      \langle 223 \rangle n = A,T,C or G
      <400> 369
                                                                         60
gcgagnnggg cgccaagcgc ggggccggag cggccttccc ggagtccttt gcgcggcacc
tggcgacaaa atggctgccc gagggagacg ggcggagcct cagggccggg aggctccggg
                                                                        120
ccccgcgggc ggtggcggtg gcgggagccg ttgggctgag tcgggatcgg ggac
                                                                        174
      <210> 370
      <211> 375
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(375)
      <223> n = A, T, C or G
      <400> 370
                                                                         60
tgcttttcca actttattta gaaaaacaaa tccaggtccc agtgccccct gtaccctccc
cgaccccagc cataatttaa ataacttana gacagagttg gagggagggg acagganagg
                                                                        120
                                                                        180
ttggggtcac ggtggaagga ggaaganagc ccactacagc cgccgcagcg cccgcttctt
gtccgtcttt ttcttggccg ccagcttctt atcgcgctcg ccagcatgct tnttggccat
                                                                        240
                                                                        300
gggaccetca geceeteeg ggeeeetgg ggeeeeaggg teggtggagg aagetteagt
                                                                        360
gccactggcc agggcccgac cggcttcggc cctgccgctg ggcccgccgg cgcccccgtg
                                                                        375
gatctctgtg agcag
      <210> 371
      <211> 375
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(375)
      <223> n = A, T, C or G
      <400> 371
                                                                          60
taaattctaa aaaatatttt aatacttgaa aacttctaaa acaaaaggta aggtaacatg
                                                                         120
ttctttcaaa agtgaatttc acatgcaaac cattaattat atttatttta ctgngagata
                                                                         180
aaagcaaaac ataacattcg gagaaagaga ccagtaactg acctatttat tttatattat
attaatgnga atcctcatta gaaatgtgat aacgttattg cacaaacaaa accgtgggca
                                                                         240
                                                                         300
gaaacatccc agcaatgcag gggcgcccat accgggttac aagggatgtc cagcatgtgt
ttccctggaa cactcanagt ctgcactttt cctgcaaatg ggaccatgtc tgattattta
                                                                         360
```

..

ttatgaaaga acact	375
<210> 372 <211> 164 <212> DNA <213> Homo sapien	
<220> <221> misc_feature <222> (1)(164) <223> n = A,T,C or G	
<pre>&lt;400&gt; 372 cgctctgtnt cctcaacctc tacctggcgg aggttatatg taaagtcaga tgtgccactg aacttgacag acacaaaatt ctactgcatt tgggctttat aatggcaagc ctgctctttt tagtggtgaa cttgacttgc gcaatgctag ttcatggaga tgtc</pre>	60 120 164
<210> 373 <211> 401 <212> DNA <213> Homo sapien	
<pre>&lt;400&gt; 373  gcgctgttcg cctttgccta cctgcagctg tggcggctgc tcctgtaccg cgagcggcgg ctgagttacc agagcctctg cctcttcctc tgtctcctgt gggcagcgct caggaccacc ctcttctccg ccgccttctc gctcagcggc tccctgcct tgctccggcc gccgctcac ctgcacttct tcccccactg gctgctctac tgctcccct cctgtctcca gttctccac ctctgctccc tcaacctcta cctggcggag gttatatgta aagtcagatg tgccactgaa cttgacagac acaaaattct actgcatttg ggcttataa tggcaagcct gctctttta gtggtgaact tgacttgcgc aatgctagtt catggagatg t</pre>	60 120 180 240 300 360 401
<210> 374 <211> 401 <212> DNA <213> Homo sapien	
<pre>&lt;400&gt; 374 ggaatgatac cattcagatt gatttggaga ctggcaagat tactgattc atcaagttcg acactggtaa cctgtgtatg gtgactggag gtgctaacct aggaagaatt ggtgtgatca ccaacagaga gaggcaccct ggatcttttg acgtggttca cgtgaaagat gccaatggca acagctttgc cactcgactt tccaacattt ttgttattgg caagggcaac aaaccatgga tttctcttcc ccgaggaaag ggtatccgcc tcaccattgc tgaagagag gacaaaagac tggcggccaa acagagcagt gggtgaaatg ggtccctggg tgacatgtca gatcttgta cgtaattaaa aatattgtgg caggattaat agcaaaaaaaa a</pre>	60 120 180 240 300 360 401
<210> 375 <211> 401 <212> DNA <213> Homo sapien	
<400> 375 gagcggagtc cgctggctga cccgagcgct ggtctccgcc gggaaccctg gggcatggag aggtctgagt acctcggccg cggcgcacgc tgcatcgcgg agccaggccg aggacgtgag ggtggagggc tcctttcccg tgaccatgct tccgggagac ggtgtggggc ctgagctgat	60 120 180

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gcacgccgtc aaggaggtgt tcaaggctgc cgctgtccca gtggagttcc aggagcacca
                                                                        240
cctgagtgag gtgcagaata tggcatctga ggagaagctg gagcaggtgc tgagttccat
                                                                        300
gaaggagaac aaagtggcca tcattggaaa gattcatacc ccgatggagt ataaggggga
                                                                        360
gctagcctcc tatgatatgc ggctgaggcg taagttggac t
                                                                        401
      <210> 376
      <211> 284
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(284)
      <223> n = A, T, C or G
      <400> 376
ggaacaaggt cgtgaaaaaa aaggtcttgg tgaggtgccg ccatttcatc tgtcctcatt
                                                                        60
ctctgcgcct ttcgcagagc ttccancagc tggtatgttg ggccagagca tccggaggtt
                                                                        120
cacaacctct gtggtccgta ggagccacta tgaggagggc cctgggaaga atttgccatt
                                                                       180
ttcagtggaa aacaagtggt cgttactagc taagatgtgt ttgtactttg gatctgcatt
                                                                       240
tgctacaccc ttccttgtan taagacacca actgcttaaa acat
                                                                       284
      <210> 377
      <211> 401
      <212> DNA
      <213> Homo sapien
      <400> 377
atttatgtta ttgcactctc ggtgtgattt atcgtatgta tctgataggt tttatgaatt
                                                                        60
gttttgagtt gtaaactcct atacccttta ttaaaatgga cctaattaag tgatttatgc
                                                                       120
tttgtgcaat ttcttaaatc agatctctct aggattgaag ggatccatag gtatctttca
                                                                       180
cttagtgtga agcctagtag tatactttta tattcctgaa gagagaccag cattaacata
                                                                       240
aagagagaag tottaggaaa aaatatacot aagaattatt tttaaaatto atactgtgaa
                                                                       300
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gtgaacgtgg tatcaccatt gatatctcct tgtggaaatt tgagaccagc aagtactatg
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gatatcaccc ccatgatggg tgtcctggac ggtgtcctaa tggaactgca agactgtgcc
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gatgtggcca ttcttgtggg ctccatgcca agaagggaag gcatggagag aaaagattta
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aagacggccg caaagaaaaa tgacaaagag gcagcaggag agggcccagc cctgtatgag
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qacccccaq atcaqaaaac ctcacccaqt qqcaaacctq ccacactcaa qatctqctct
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tggaatgtgg atgggcttcg agcctggatt aagaagaaag gattagattg ggtaaaggaa
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cccgccgctg tgcattgcag cattatttca gttcaaaatg aactatatgc ctggcaccgc
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cagecteate gaggaeattg acaaaaagea ettggttetg ettegagatg gaaggaeaet
tataggettt ttaagaagea ttgateaatt tgeaaaetta gtgetaeate agaetgtgga
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gcgtattcat gtgggcaaaa aa agaaaatgtg gtcctactag ga gcaagtatcc attgaagaaa ttagcagagaag t	agaaataga cttggaaaag	gagagtgaca	caccecteca ccaagetgga	360 420 480 491
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                                                                       180
actgcatttt acaaaattga aacttggaag ctgtattaac ttttatagtt aaacattgta
                                                                       240
                                                                       300
ttaaataaac tatactataa taaacagttt ggttttgtat tttttaaatt gtattatcca
                                                                       360
gccttttaaa aattaaaagc taaataatga aaataaacca attaaaacat acttttactc
                                                                       420
tcagatatac aggtatttac attatgaaaa aactgaacaa agttttaaca atactgagct
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                                                                       491
aatcataata c
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                                                                       420
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180

360

420

480

511

1984

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attt

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ccacgeeegg egggggeage ggaggeggag gegeegtege tgeageetea ggegeegegg 240
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tettececca etggetgete tactgettee ceteetgtet ecagttetee acqetetgte 540
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<210> 391
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<212> PRT

<213> Homo sapien

<400> 391

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Val Ala Ala Ser Gly Ala Ala Val Pro Gly Ser Val Gln Leu Ala 35 40 45

Leu Ser Val Leu His Ala Leu Leu Tyr Ala Ala Leu Phe Ala Phe Ala 50 55 60

Tyr Leu Gln Leu Trp Arg Leu Leu Leu Tyr Arg Glu Arg Arg Leu Ser
65 70 75 80

Tyr Gln Ser Leu Cys Leu Phe Leu Cys Leu Leu Trp Ala Ala Leu Arg 85 90 95

Thr Thr Leu Phe Ser Ala Ala Phe Ser Leu Ser Gly Ser Leu Pro Leu 100 105 110

Leu Arg Pro Pro Ala His Leu His Phe Pro His Trp Leu Leu Tyr 115 120 125

Cys Phe Pro Ser Cys Leu Gln Phe Ser Thr Leu Cys Leu Leu Asn Leu 130 135 140

Tyr Leu Ala Glu Val Ile Cys Lys Val Arg Cys Ala Thr Glu Leu Asp 150 155 160

Arg His Lys Ile Leu Leu His Leu Gly Phe Ile Met Ala Ser Leu Leu 165 170 175

Phe Leu Val Val Asn Leu Thr Cys Ala Met Leu Val His Gly Asp Val 180 185 190

Pro Glu Asn Gln Leu Lys Trp Thr Val Phe Val Arg Ala Leu Ile Asn 195 200 205

Asp Ser Leu Phe Ile Leu Cys Ala Ile Ser Leu Val Cys Tyr Ile Cys 210 215 220

Lys Ile Thr Lys Met Ser Ser Ala Asn Val Tyr Leu Glu Ser Lys Gly 225 230 235 240

Met Ser Leu Cys Gln Thr Val Ile Val Gly Ser Val Val Ile Leu Leu 245 250 255

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                            280
Lys Ala His Val Glu Asp Ile Ser Gly Glu Glu Tyr Ile Val Phe Gly
                        295
Met Val Leu Phe Leu Trp Glu His Val Pro Ala Trp Ser Val Val Leu
305
                    310
                                        315
Phe Phe Arg Ala Gln Arg Leu Asn Gln Asn Leu Ala Pro Ala Gly Met
                                    330
                325
Ile Asn Ser His Ser Tyr Ser Ser Arg Ala Tyr Phe Phe Asp Asn Pro
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                                345
                                                     350
Arg Arg Tyr Asp Ser Asp Asp Leu Pro Arg Leu Gly Ser Ser Arg
                            360
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Glu Gly Ser Leu Pro Asn Ser Gln Ser Leu Gly Trp Tyr Gly Thr Met
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Thr Gly Cys Gly Ser Ser Ser Tyr Thr Val Thr Pro His Leu Asn Gly
Pro Met Thr Asp Thr Ala Pro Leu Leu Phe Thr Cys Ser Asn Leu Asp
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1584

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Ser Glu Met Ile Glu Thr Gln Glu Asp Ile Tyr Val Gly Ser Ile Glu
         35
                             40
                                                 4.5
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Leu Arg Asp Gly Ala Glu Leu Pro Arg His Cys Phe Ser Cys Thr Asp
                     70
Gly Tyr Val Leu Val Tyr Ser Thr Asp Ser Arg Glu Ser Phe Gln Arg
                 85
Val Glu Leu Leu Lys Lys Glu Ile Asp Lys Ser Lys Asp Lys Lys Glu
                                105
Val Thr Ile Val Val Leu Gly Asn Lys Cys Asp Leu Gln Glu Gln Arg
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                            120
                                                125
Arg Val Asp Pro Asp Val Ala Gln His Trp Ala Lys Ser Glu Lys Val
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                        135
Lys Leu Trp Glu Val Ser Val Ala Asp Arg Arg Ser Leu Leu Glu Pro
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Phe Val Tyr Leu Ala Ser Lys Met Thr Gln Pro Gln Ser Lys Ser Ala
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Gly Arg Lys Val Gln Ser Gly Asn Ile Asn Ala Ala Lys Thr Ile Ala
Asp Ile Ile Arg Thr Cys Leu Gly Pro Lys Ser Met Met Lys Met Leu
Leu Asp Pro Met Gly Gly Ile Val Met Thr Asn Asp Gly Asn Ala Ile
                    70
                                        75
Leu Arg Glu Ile Gln Val Gln His Pro Ala Ala Lys Ser Met Ile Glu
Ile Ser Arg Thr Gln Asp Glu Glu Val Gly Asp Gly Thr Thr Ser Val
                               105
Ile Ile Leu Ala Gly Glu Met Leu Ser Val Ala Glu His Phe Leu Glu
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                           120
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- Gln Gln Met His Pro Thr Val Val Ile Ser Ala Tyr Arg Lys Ala Leu 130 135 140
- Asp Asp Met Ile Ser Thr Leu Lys Lys Ile Ser Ile Pro Val Asp Ile 145 150 155 160
- Ser Asp Ser Asp Met Met Leu Asn Ile Ile Asn Ser Ser Ile Thr Thr
  165 170 175
- Lys Ala Ile Ser Arg Trp Ser Ser Leu Ala Cys Asn Ile Ala Leu Asp 180 185 190
- Ala Val Lys Met Val Gln Phe Glu Glu Asn Gly Arg Lys Glu Ile Asp 195 200 205
- Ile Lys Lys Tyr Ala Arg Val Glu Lys Ile Pro Gly Gly Ile Ile Glu 210 215 220
- Asp Ser Cys Val Leu Arg Gly Val Met Ile Asn Lys Asp Val Thr His 225 230 235 240
- Pro Arg Met Arg Arg Tyr Ile Lys Asn Pro Arg Ile Val Leu Leu Asp 245 250 255
- Ser Ser Leu Glu Tyr Lys Lys Gly Glu Ser Gln Thr Asp Ile Glu Ile 260 265 270
- Thr Arg Glu Glu Asp Phe Thr Arg Ile Leu Gln Met Glu Glu Glu Tyr 275 280 285
- Ile Gln Gln Leu Cys Glu Asp Ile Ile Gln Leu Lys Pro Asp Val Val 290 295 300
- Ile Thr Glu Lys Gly Ile Ser Asp Leu Ala Gln His Tyr Leu Met Arg 305 310 315 320
- Ala Asn Ile Thr Ala Ile Arg Arg Val Arg Lys Thr Asp Asn Asn Arg 325 330 335
- Ile Ala Arg Ala Cys Gly Ala Arg Ile Val Ser Arg Pro Glu Glu Leu 340 345 350
- Arg Glu Asp Asp Val Gly Thr Gly Ala Gly Leu Leu Glu Ile Lys Lys 355 360 365
- Ile Gly Asp Glu Tyr Phe Thr Phe Ile Thr Asp Cys Lys Asp Pro Lys 370 375 380
- Ala Cys Thr Ile Leu Leu Arg Gly Ala Ser Lys Glu Ile Leu Ser Glu 385 390 395 400
- Val Glu Arg Asn Leu Gln Asp Ala Met Gln Val Cys Arg Asn Val Leu
  405 410 415

Leu Asp Pro Gln Leu Val Pro Gly Gly Gly Ala Ser Glu Met Ala Val 420 425 430

Ala His Ala Leu Thr Glu Lys Ser Lys Ala Met Thr Gly Val Glu Gln 435 440 445

Trp Pro Tyr Arg Ala Val Ala Gln Ala Leu Glu Val Ile Pro Arg Thr 450 460

Leu Ile Gln Asn Cys Gly Ala Ser Thr Ile Arg Leu Leu Thr Ser Leu 465 470 475 480

Arg Ala Lys His Thr Gln Glu Asn Cys Glu Thr Trp Gly Val Asn Gly
485 490 495

Glu Thr Gly Thr Leu Val Asp Met Lys Glu Leu Gly Ile Trp Glu Pro 500 505 510

Leu Ala Val Lys Leu Gln Thr Tyr Lys Thr Ala Val Glu Thr Ala Val 515 520 525

Leu Leu Arg Ile Asp Asp Ile Val Ser Gly His Lys Lys Gly 530 535 540

Asp Asp Gln Ser Arg Gln Gly Gly Ala Pro Asp Ala Gly Gln Glu 545 550 555

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<211> 307

<212> PRT

<213> Homo sapiens

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Arg Ile Leu Glu Ser Ser Pro Gly Val Thr Glu Val Thr Ile Ile Glu 35 40 45

Lys Pro Pro Ala Glu Arg His Met Ile Ser Ser Trp Glu Gln Lys Asn 50 55 60

Asn Cys Val Met Pro Glu Asp Val Lys Asn Phe Tyr Leu Met Thr Asn 65 70 75 80

Gly Phe His Met Thr Trp Ser Val Lys Leu Asp Glu His Ile Ile Pro 85 90 95

Leu Gly Ser Met Ala Ile Asn Ser Ile Ser Lys Leu Thr Gln Leu Thr 100 105 110

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                                                 125
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Phe Asp Ser Arg Ser Val Ile Phe Glu Leu Asp Ser Cys Asn Gly Ser
                    150
                                         155
Gly Lys Val Cys Leu Val Tyr Lys Ser Gly Lys Pro Ala Leu Ala Glu
                165
                                     170
Asp Thr Glu Ile Trp Phe Leu Asp Arg Ala Leu Tyr Trp His Phe Leu
            180
                                 185
Thr Asp Thr Phe Thr Ala Tyr Tyr Arg Leu Leu Ile Thr His Leu Gly
        195
                             200
Leu Pro Gln Trp Gln Tyr Ala Phe Thr Ser Tyr Gly Ile Ser Pro Gln
    210
                        215
Ala Lys Gln Trp Phe Ser Met Tyr Lys Pro Ile Thr Tyr Asn Thr Asn
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Leu Leu Thr Glu Glu Thr Asp Ser Phe Val Asn Lys Leu Asp Pro Ser
Lys Val Phe Lys Ser Lys Asn Lys Ile Val Ile Pro Lys Lys Lys Gly
            260
                                 265
Pro Val Gln Pro Ala Gly Gly Gln Lys Gly Pro Ser Gly Pro Ser Gly
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Pro Ser Thr Ser Ser Thr Ser Lys Ser Ser Ser Gly Ser Gly Asn Pro
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                                             300
Thr Arg Lys
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geogeteect gggetatgee taegneaact tecaneaace ggeogaeget gategggett 180
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cgcaaccatg agcagegagg ccgagaccca gcagecgccc gccgccccc cccgccgccc 180
cegeceteag egeegeegae aceaageeeg geactaeggg eageggegea gggageggtg 240
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aggttttggg aacagtaaaa tggttcaatg taaggaacgg atatggtttc atcaacagga 360
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gatactecte acctgetect tgaatgacag egecacagag gteacaggge accgetgget 180
gaaggggggc gtggtgctga aggaggacgc gctgcccggc cagaaaacgg agttcaaggt 240
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<211> 416
<212> DNA
<213> Homo sapiens
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gccgtctact tcaaggagca gtttctggac ggagacgggt ggacttcccg ctggatcgaa 180
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<210> 407
<211> 423
<212> DNA
<213> Homo sapiens
<400> 407
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<211> 423
<212> DNA
<213> Homo sapiens
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<213> Homo sapiens
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aggaagaaan gccagaacca gacataagtt cagaggaatc tgtctccact gtagaagaac 420
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aaga
```

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<211> 430
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<213> Homo sapiens
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<213> Homo sapiens
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gaaagacttg atgaaatatt tcagacagga ttggtagctt atgtcgatct tgatgaaaga 240
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gaagcgaag
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<211> 398
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(398)
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gaaaagaatc tcaaagtact ttgagaatca ctacaagaaa aactccttgt ggtgaaggtt 300
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<211> 269
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Asn Gly Pro Arg Ser Gly Leu Ile Ser Val Ala Ile Thr Leu His Pro

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- Phe Arg Glu Leu Pro Asn Pro Leu Leu Thr Tyr Gln Leu Tyr Glu Lys
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- Phe Ser Asp Ala Val Ser Ala Ala Thr Asp Glu Glu Arg Leu Ile Lys 85 90 95
- Ile His Asp Val Ile Gln Gln Leu Pro Pro Pro His Tyr Arg Thr Leu 100 105 110
- Glu Phe Leu Met Arg His Leu Ser Leu Leu Ala Asp Tyr Cys Ser Ile 115 120 125
- Thr Asn Met His Ala Lys Asn Leu Ala Ile Val Trp Ala Pro Asn Leu 130 135 140
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870

875

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- Arg Thr His Arg Thr Asn Arg Pro Leu Pro Pro Pro Pro Ser Gln Arg 915 920 925
- Ser Ala Glu Gln Pro Pro Val Val Gly Gln Val Gln Ala Ala Thr Asn 930 935 940
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- Glu Arg Pro Pro Glu Pro Arg Ala Met Asp Asp Pro Ala Ser Ala Phe 965 970 975
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Phe Glu Ala Arg Ile Ala Leu Leu Pro Leu Leu Gln Ala Glu Thr Asp 85 90 95

Arg Arg Thr Leu Gln Met Leu Arg Glu Asn Leu Glu Glu Glu Ala Ile 100 105 110

Ile Met Lys Asp Val Pro Asp Trp Lys Val Gly Glu Ser Val Phe His 115 120 125

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Phe Ala Pro Trp Cys Gly His Cys Gln Arg Leu Gln Pro Thr Trp Asn 50 55 60

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Val Lys Tyr Gln Gly Pro Arg Asp Phe Gln Thr Leu Glu Asn Trp Met 115 120 125

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Gln Leu Gln Arg Thr Glu Thr Gly Ala Thr Glu Thr Val Thr Pro Ser 260 265 270

Glu Ala Pro Val Leu Ala Ala Glu Pro Glu Ala Asp Lys Gly Thr Val 275 280 285

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Thr Phe Ile Lys Phe Tyr Ala Pro Trp Cys Gly His Cys Lys Thr Leu 305 310 315 320

Ala Pro Thr Trp Glu Glu Leu Ser Lys Lys Glu Phe Pro Gly Leu Ala 325 330 335

Gly Val Lys Ile Ala Glu Val Asp Cys Thr Ala Glu Arg Asn Ile Cys 340 345 350

Ser Lys Tyr Ser Val Arg Gly Tyr Pro Thr Leu Leu Leu Phe Arg Gly 355 360 365

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Glu Ser Val Cys Leu Asp Arg Cys Val Ser Lys Tyr Leu Asp Ile His 50 55 60

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35 40 45

Asn Leu Tyr Pro Arg Leu Tyr Pro Glu Leu Ser Gln Tyr Met Gly Leu 50 55 60

Ser Leu Asn Glu Glu Glu Ile Arg Ala Asn Val Ala Val Val Ser Gly
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Ala Pro Leu Gln Gly Gln Leu Val Ala Arg Pro Ser Ser Ile Asn Tyr

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Ser 225	Ile	Val	Lys	Asp	Ser 230	Ser	Ala	Ala	Arg	Asn 235	Gly	Leu	Leu	Thr	Glu 240
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- Gln Asp Gly Leu Gln Ile Thr Val Asn Gly Thr Val Leu Ser Ser 50 55 60
- Gly Thr Arg Phe Ala Val Asn Phe Gln Thr Gly Phe Ser Gly Asn Asp 65 70 75 80
- Ile Ala Phe His Phe Asn Pro Arg Phe Glu Asp Gly Gly Tyr Val Val 85 90 95
- Cys Asn Thr Arg Gln Asn Gly Ser Trp Gly Pro Glu Glu Arg Lys Thr
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- His Met Pro Phe Gln Lys Gly Met Pro Phe Asp Leu Cys Phe Leu Val
- Gln Ser Ser Asp Phe Lys Val Met Val Asn Gly Ile Leu Phe Val Gln 130 135 140
- Tyr Phe His Arg Val Pro Phe His Arg Val Asp Thr Ile Ser Val Asn 145 150 155 160
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- Phe Pro Pro Arg Pro Arg Gly Arg Arg Gln Lys Pro Pro Gly Val Trp 195 200 205
- Pro Ala Asn Pro Ala Pro Ile Thr Gln Thr Val Ile His Thr Val Gln 210 215 220
- Ser Ala Pro Gly Gln Met Phe Ser Thr Pro Ala Ile Pro Pro Met Met 225 230 235 240
- Tyr Pro His Pro Ala Tyr Pro Met Pro Phe Ile Thr Thr Ile Leu Gly 245 250 255
- Gly Leu Tyr Pro Ser Lys Ser Ile Leu Leu Ser Gly Thr Val Leu Pro 260 265 270
- Ser Ala Gln Arg Phe His Ile Asn Leu Cys Ser Gly Asn His Ile Ala 275 280 285
- Phe His Leu Asn Pro Arg Phe Asp Glu Asn Ala Val Val Arg Asn Thr 290 295 300
- Gln Ile Asp Asn Ser Trp Gly Ser Glu Glu Arg Ser Leu Pro Arg Lys 305 310 315 320

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